ARIZONA NEWBORN SCREENING PROGRAM

GUIDELINES

Division of Public Health Services

Arizona Department of Health Services

August 2003

Office of Women's & Children's Health

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This document can also be downloaded in PDF format from
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http://www.hs.state.az.us/phs/owch/newbrnscrn.htm

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1.1 Program Background and Description

For many types of genetic or metabolic disease, early diagnosis and treatment are critical. Although babies born with these disorders may appear to be normal at birth, with time the disorder may have a devastating or lethal effect on the infant's health and development. Early screening, detection and treatment of these disorders can, in most cases, result in normal growth and development.

Arizona has been conducting widespread newborn screening for certain types of genetic disorders since 1979. A laboratory in Colorado originally performed screening tests for all Arizona newborns.

In 1993, the Arizona Legislature enacted laws requiring the Arizona Department of Health Services to develop and administer a formal Newborn Screening Program. The Arizona Newborn Screening Program was created within the Office of Women's and Children's Health, in the Division of Public Health Services. The Program has enabled the Department to enhance its public health role in the newborn screening process, obtain more timely results from screening, and promote better follow-up for suspected or confirmed cases.

The Newborn Screening Program conducts newborn screening tests for eight (8) disorders. These particular disorders have been selected because their detection and treatment in the newborn period is effective in preventing severe morbidity or mortality. They are:

1. Congenital Hypothyroidism
2. Congenital Adrenal Hyperplasia
3. Phenylketonuria (PKU)
4. Galactosemia
5. Biotinidase Deficiency
6. Maple Syrup Urine Disease
7. Homocystinuria
8. Hemoglobinopathy

For most of these disorders, the incidence in the population is rare, but the potential for devastating consequences and the high costs of treating infants who do have the disorders is thought to justify the cost of mass screening.

The Department contracts with the Arizona State Laboratory to perform screening tests for these disorders. Fees charged for the testing are used to support the operation of the Newborn Screening Program.

1.2 Program Goal

The goal of the Arizona Newborn Screening Program is to identify all infants with selected disorders, and ensure that the affected newborns receive appropriate and timely treatment to prevent serious medical problems.

1.3 Overview of Key Roles

The success of the Newborn Screening Program depends upon the coordinated efforts of many health care professionals.

1. Practitioners, Hospitals, and Laboratories

Practitioners (physicians, nurse midwives, lay midwives, primary care providers) are generally responsible for: ordering the screening tests for newborn infants in their care, informing parents about the screening tests, and collection and handling of newborn screening specimens. Practitioners, and/or their contracted laboratories, may collect and send specimens for testing. Practitioners and designated hospitals and laboratories work together to coordinate timely collection and delivery of acceptable newborn screening specimens to the central screening laboratory.

2. Central Screening Laboratory

As per A.R.S.§36-694, a laboratory in Arizona is awarded a contract from the Department to be the central screening laboratory for newborn screening. Currently, the central screening laboratory is the Arizona State Laboratory (State Lab). The State Lab receives all Arizona newborn screening specimens for testing for the eight (8) disorders. Staff there review the specimens for acceptability, perform laboratory testing, keep records of the tests performed, mail reports of results to submitters and physicians and conduct quality control studies of laboratory methods and practices. The State Lab also bills for the testing of specimens (See Chapter 7).

3. Arizona Department of Health Services - Newborn Screening Program

As per A.R.S.§36-694, the Department is responsible for the overall development, implementation, management and evaluation of the Newborn Screening Program. The Newborn Screening Program Manager is responsible for the administration

and coordination of program operations. The Department monitors the performance of the contracted laboratory and oversees the collection of revenues from the screening tests. The Health Educator, often in conjunction with the State Lab's Quality Assurance personnel, is responsible for providing education to the medical community and public. In addition, the Program Manager coordinates resource networks for the specialized treatment and medical management of identified newborn screening disorders, as well as other program consultants and contractors.

The Program Manager also administers the Follow-up component of the Newborn Screening Program. The Follow-up staff have many responsibilities, including, but not limited to: reporting of positive results to physicians and parents, tracking infants with positive results to help them get into appropriate care, monitoring and evaluating the system, monitoring confirmatory testing, and maintaining a registry of confirmed cases.

4. Neometrics Data Management System

The Department's Newborn Screening Program currently utilizes software from Neometrics, Incorporated, for its data management system. The Neometrics System is a computerized data management system that has the capacity to automate many of the administrative tasks necessary to operate the Newborn Screening Program. The Neometrics system has two primary components, a laboratory component (MSDS - Metabolic Screening Database System) and a case management follow-up component (CMS - Case Management System).

The MSDS allows laboratory personnel at the State Lab to enter demographic data obtained from specimen collection kits, to keep track of physician/submitter contact information, and to associate entry of laboratory results with the specific demographic information. A component of it is also used in generating invoices for submitters of first specimens. Based on criteria, standards, and policy established by the Department's Newborn Screening Program, computerized mailers are generated from the MSDS to hospital submitters and physicians to report screening results.

The State Lab reports abnormal screening test results to the Follow-up staff of the Newborn Screening Program, through electronic transfer from the MSDS to the CMS. For highly abnormal results, staff at the State Lab (according to defined protocol) will also report the results by telephone. The members of the Follow-up staff use the information in the CMS to notify physicians and parents of infants with abnormal test results, and use it as a registry of confirmed cases. They also use data in the MSDS on a daily basis to check on the presence and status of specimens for babies.

1.4 How To Use These Guidelines

The Newborn Screening Guidelines is a reference and information resource designed especially for any person in Arizona who provides medical care, nursing, laboratory, or diagnostic services to newborn infants and their families. The Department encourages all health care professionals who provide services to newborn infants to familiarize themselves with this document, and refer to it when needed.

This document contains information that will answer many of your questions about the Newborn Screening Program, including specific information about how to collect and submit newborn screening specimens. If you have questions that are not answered in this manual, or if you have suggestions for additional information that can be included, please contact the Department's Newborn Screening Program Manager at the following address:

Newborn Screening Program Manager
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Arizona Department of Health Services
150 North 18th Avenue, Suite 320
Phoenix, AZ 85007
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CHAPTER 2
GLOSSARY

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ARIZONA STATE LABORATORY

The Department contracts with the Arizona State Laboratory (State Lab) to perform laboratory tests for the eight disorders that comprise the Arizona newborn screening test panel. All Arizona newborn screening specimens are sent here for testing. The State Lab also performs tests for one specific disorder on specimens requested in response to a prior abnormal screening. The State Lab reports test results to physicians, hospital submitters and follow-up staff, and performs a variety of other functions.

BIOTINIDASE DEFICIENCY

Biotinidase deficiency is one of the eight disorders screened for by the Newborn Screening Program. Biotinidase is an enzyme that liberates biotin, an essential vitamin cofactor, from a bound form to one that can be used by the body. Deficiency of this enzyme results in improper functioning of several critical, biotin-requiring enzyme systems. Biotinidase deficiency is a genetic, congenital, metabolic disorder that can cause severe neurological impairment, coma, and death, if undetected. Early detection and treatment with therapeutic doses of biotin can greatly improve a child's prognosis for normal growth and development. Refer to Section 4.6 for more information on biotinidase deficiency.

CHILDREN'S REHABILITATIVE SERVICES

Children's Rehabilitative Services (CRS) is a program administered by the Department to provide rehabilitative medical care and services to infants and children with special health care needs, using a multidisciplinary approach. All of the disorders detected through the Newborn Screening Program may be treated through enrollment in CRS. Families must meet medical and financial eligibility requirements to receive CRS services.

CONFIRMATORY TEST

A confirmatory test is a laboratory test that is done to verify or rule out the presence of a disorder. The newborn screening tests are "screening tests" that identify the likelihood of illness, but do not provide diagnostic confirmation. Because some disorders may produce the same screening results as one of the eight disorders in the screening panel but arise from different causes and present different symptoms, additional tests are often needed to determine what disorder an infant really has and what treatments are necessary.

Depending upon the abnormal test result, it may be necessary to initiate treatment as soon as possible, without waiting for confirmation of a disorder.

CONGENITAL ADRENAL HYPERPLASIA

Congenital adrenal hyperplasia (CAH) is one of the eight disorders screened for by the Newborn Screening Program. The Newborn Screening Program tests for 21-hydroxylase (21-OHase) deficiency, the most common enzymatic defect causing CAH. CAH is an endocrine disorder in which the adrenal glands produce an inadequate amount of the hormones cortisol and sometimes aldosterone. Infants lacking aldosterone will lose large amounts of salt in their urine and perspiration. In addition to the decreased levels of cortisol and aldosterone, there is an increased production of a class of male sex hormones called androgens. While the male fetus is not obviously affected, the female fetus may be born with ambiguous genitalia. This can result in incorrect gender assignment of virilized females as males. Left untreated, CAH causes excess virilization, rapid growth with accelerated skeletal maturation, short stature, salt-losing syndrome and possible death. In the salt wasting form of CAH, an infant can have a crisis within the first 5 days to several months of life. Treatment consists of cortisol replacement, mineral corticoid treatment and salt supplementation. Refer to Section 4.7 for more information on congenital adrenal hyperplasia.

CONGENITAL HYPOTHYROIDISM

Congenital hypothyroidism (CH) is one of the eight disorders screened for by the Newborn Screening Program. It occurs in infants who are born with an inability to produce sufficient amounts of the thyroid hormone, thyroxine. Thyroxine is essential for regulating the normal function of all body organs, and is a substance that is essential for normal brain development. Many infants will appear to be clinically normal until approximately 3 months of age. By the time symptoms develop, brain damage will have already occurred. Effective treatment consists of lifelong daily administration of thyroid hormone. Refer to Section 4.1 for more information on congenital hypothyroidism.

DEPARTMENT

"Department" means the Arizona Department of Health Services. This is the state agency responsible for administering public health services and a variety of community health programs, including the Newborn Screening Program.

DIRECTOR

The Director of the Department is designated as the Chairman of the Newborn Screening Program Committee, and is responsible for the establishment of the Newborn Screening Program within the Department, including development of administrative rules (Arizona

Administrative Code) to govern the program, per Arizona Revised Statutes (ARS § 36-694 and § 36-694.01).

FIRST SCREEN

The first screen is the first acceptable specimen tested for the eight disorders on the newborn screening panel. The specimen for the first screen is collected, ideally, 48 to 72 hours after birth, but should be collected prior to a transfusion, prior to administration of antibiotics and prior to discharge from the hospital. If the birth occurs outside the hospital, the attending physician, nurse, midwife, or licensed midwife attending the birth is responsible for ordering the test. In any case, it should be collected no later than 7 days of age.

FOLLOW-UP STAFF

The Department's Newborn Screening Program Follow-up staff is responsible for coordinating information, follow-up, and referral services for families of infants with positive screens. Refer to Section 6 for more information about the responsibilities of personnel.

GALACTOSEMIA

Galactosemia is one of the eight disorders screened for by the Newborn Screening Program. Galactosemia is a genetic, congenital, metabolic disorder. The Newborn Screening Program tests for classic galactosemia, which results in elevated blood galactose levels due to a deficiency in galactose-1-phosphate uridyl transferase (GALT), one of three enzymes in the galactose catabolic pathway. Galactose is a component of lactose, which is the principal carbohydrate found in mammalian milk and non-soy commercial infant formulas. Infants with improper metabolism of galactose, as a result of this enzyme deficiency, may develop liver damage, cataracts, jaundice, lethargy, and mental retardation. Death may result from sepsis within one to two weeks of life. Treatment includes strict dietary exclusion of products containing galactose. Refer to Section 4.3 for more information on classic galactosemia.

HEALTH EDUCATOR

The Health Educator is a part of the Arizona Newborn Screening Program staff and is responsible for providing information to the professional health care and lay communities about the Arizona Newborn Screen Program. This individual also represents the Arizona Newborn Screening Program at conferences, seminars and health fairs. Other responsibilities include developing, or participating in the development of, educational

materials in the form of brochures, fact sheets, videos and public service announcements, as well as Quality Assurance tasks.

HEMOGLOBINOPATHY

The term hemoglobinopathy refers to any of a large family of inherited genetic disorders of hemoglobin and is one of the eight disorders screened for by the Newborn Screening Program. Hemoglobin is a complex protein within red blood cells and is responsible for transporting oxygen to body tissues. Hemoglobinopathies fall into three major types: structural variations in hemoglobin; thalassemias (reduced rates of synthesis of proteins that comprise hemoglobin); and hereditary persistence of fetal hemoglobin. Hemoglobinopathies represent the single most common genetic disorder in the human population. Sickle cell anemia, one type of hemoglobinopathy, is caused by a variation in the structure of hemoglobin. Refer to Section 4.8 for more information on sickle cell anemia and other hemoglobinopathies.

HOMOCYSTINURIA

Homocystinuria is one of the eight disorders screened for by the Newborn Screening Program. Homocystinuria is a genetic, congenital, metabolic disorder of methionine metabolism. The disorder is caused by the elevation of homocystine and methionine due to the lack of cystathionine-β-synthetase activity. Although there are no clinical symptoms of this disorder in the newborn period, children may later develop seizure disorders, liver and neurological damage, cataracts and dislocated lenses, osteoporosis and connective tissue damage. Treatment is aimed at providing high doses of vitamin B6 (to increase enzyme activity) or restricting methionine in the diet. Refer to Section 4.4 for more information on homocystinuria.

HYPERPHENYLALANINEMIA

Hyperphenylalaninemia is a variant form of phenylketonuria (PKU). This is a condition in which the plasma phenylalanine (phe) levels are lower than in classic PKU but are higher than in the general population. Blood phenylalanine levels may steadily increase with age, requiring medical treatment later in life. Mild mental impairment may occur, depending on the degree and duration of the increase in plasma phenylalanine levels. Due to the risk of irreversible damage, all infants with persistently abnormal levels of phenylalanine should receive special blood and urine tests on a regular basis. Refer to Section 4.2 for more information on hyperphenylalaninemia.

MAPLE SYRUP URINE DISEASE

Maple Syrup Urine Disease (MSUD) is one of the eight disorders screened for by the Newborn Screening Program. It is a genetic, congenital, metabolic disorder characterized

by the inability of the body to metabolize the branched-chain amino acids, leucine, isoleucine, and valine, due to deficient activity of branched-chain ketoacid dehydrogenase. The onset of symptoms begins shortly after birth, and includes poor feeding, lethargy, vomiting, and central nervous system depression. Coma from metabolic acidosis and death generally occur within 2 to 4 weeks. Early detection and aggressive management of symptoms, including strict dietary restriction of branched-chain amino acids, are essential to prevent or minimize life-threatening problems. Refer to Section 4.5 for more information on MSUD.

METABOLIC FORMULA

Metabolic formula includes a variety of commercially prepared dietary formulas. These special formulas are prepared to accommodate dietary restrictions required to treat metabolic disorders caused by errors in protein or carbohydrate metabolism, such as PKU, galactosemia, MSUD, and homocystinuria.

NEWBORN SCREENING PROGRAM

Arizona's Newborn Screening Program is a preventive public health program for early identification of rare disorders that can lead to death, disability, or severe retardation. The Program administers all newborn-screening activities throughout the state. These activities include testing of specimens; coordination with consulting specialists, physicians, and hospitals; follow-up of abnormal test results; education of health professionals and the general public; and monitoring of data associated with testing, billing for tests, follow-up, and educational activities.

NEWBORN SCREENING PROGRAM COMMITTEE

The Newborn Screening Program Committee was constituted under ARS 36-694. The committee is comprised of the Department's Director (Chairman) and five additional physicians, which include representation from the specialties of endocrinology, pediatrics, family practice, and obstetrics. The Committee oversees the medical management of Arizona's Newborn Screening Program.

NEWBORN SCREENING PROGRAM MANAGER

The Newborn Screening Program Manager is the staff member within the Office of Women's and Children's Health, Division of Public Health Services, in the Department who is responsible for overall program development and coordination of the Arizona Newborn Screening Program.

NEWBORN SCREENING TEST

A Newborn Screening Test consists of two screens, which are required for each newborn. Newborn screening is the process of collecting blood specimens from all newborn infants to test for certain endocrine and metabolic disorders and hemoglobinopathies. All infants must have a first specimen collected at 48 to 72 hours after birth or prior to discharge from the hospital (or discharge from the care of the practitioner who attended the birth, if the birth did not occur in the hospital). A second screen is required at 7 to 14 days of age or at the first outpatient visit to the physician. Arizona conducts newborn screening for eight disorders: 1) congenital hypothyroidism; 2) congenital adrenal hyperplasia; 3) phenylketonuria; 4) galactosemia; 5) biotinidase deficiency; 6) maple syrup urine disease; 7) homocystinuria; and 8) hemoglobinopathy.

PHENYLKETONURIA

Phenylketonuria (PKU) is one of the eight disorders screened for by the Newborn Screening Program. This is a genetic, congenital, metabolic disorder in which the body cannot properly metabolize the amino acid, phenylalanine, which is found in all dietary protein. The body lacks the enzyme phenylalanine hydroxylase, which converts phenylalanine into tyrosine. Excess levels of phenylalanine accumulate in the blood and can cause severe brain damage and retardation if left untreated. Because phenylalanine is an essential amino acid, treatment of this disorder emphasizes a low-phenylalanine diet to maintain blood levels of phenylalanine within an acceptable therapeutic range. Refer to Section 4.2 for more information on PKU.

PRACTITIONER

Also known as the “health care provider,” the practitioner is the person(s) responsible for supervising the birth of an infant, and/or the early neonatal health care of the infant. This person may be an obstetrician, midwife, pediatrician, family practitioner, or attending physician.

RECALL TEST

The recall test is a repeat filter paper dried blood spot test for a single disorder, performed in response to an abnormal or positive result on a previous newborn screening specimen.

SECOND SCREEN

The second screen is the second acceptable specimen tested for the eight disorders on the newborn screening panel. The specimen for the second screen is collected between one and two weeks of age, or at the time of the first outpatient visit to the baby’s primary care provider, whichever comes first. In Arizona, a second newborn screen is required for all

newborns. The second screen ensures detection of disorders characterized by metabolite accumulation that could be missed as a result of the first screen being done before accumulation can occur, and of disorders with delayed onset. A routine second screen at the first visit to the primary care physician also assures timely additional results for disorders that may cause rapid onset of symptoms or for which there is a high false positive rate on first screens.

SICKLE CELL DISEASE

Sickle cell disease is a complex hemoglobinopathy. It is characterized by a structural change in hemoglobin, the oxygen-carrying protein in red blood cells. These changes result in a characteristic "sickle" shape to the red blood cells. This family of sickling disorders is characterized by two major pathologic processes, anemia and vasoocclusion. Painful crises (rapid onset of pain in the limbs, back, abdomen or chest) are the result of vasoocclusive episodes. Treatment is prophylactic penicillin, pain control, rest during crisis, and avoidance of extreme oxygen deprivation or dehydration. Early detection is important to minimize complications of the disease. Refer to Section 4.8 for more information on sickle cell disease.

SPECIMEN COLLECTION KIT

The specimen collection kit is the screening form. This form serves two purposes: 1) it contains the filter paper on which the blood specimen is collected; and 2) it provides information regarding the infant, mother, physician and submitter. The specimen collector applies blood drops from an infant's heel directly to the filter paper to obtain the blood sample for all tests for the eight disorders comprising the newborn screening test panel. Title 9, Chapter 14, Article 5, R9-14-502 (B)(C) of the Arizona Administrative Register specifies what information is required on an acceptable specimen collection kit. The specimen collection kit is obtained from the Arizona State Laboratory by calling 602-542-1190. Refer to Chapter 5, Specimen Collection and Submittal, for more information on the specimen collection kits.

SPECIMEN COLLECTOR

The blood specimen collector is the person who obtains the blood sample from the infant for the newborn screening test specimen. In a hospital setting, this task is usually delegated to nursing staff or laboratory personnel by standing orders of the practitioner. In an outpatient setting, the specimen collector may include staff in a physician's office, clinic laboratory staff, staff at a laboratory contracted by the patient's insurance company, a midwife, a community health nurse and other providers.

THALASSEMIA

Thalassemia is a hemoglobinopathy characterized by impaired synthesis of one or more of the hemoglobin chains. Severity of symptoms may range from barely detectable to fatal anemia.

UNSATISFACTORY SPECIMEN

An unsatisfactory specimen is a specimen that the laboratory rejects in advance of testing, because it could provide unreliable, misleading, or clinically inaccurate values for the particular analytes being tested. The practitioner who sends such a specimen (or causes such a specimen to be sent) to the State Lab is required to ensure that another specimen is collected and submitted, as soon as possible after receiving a telephone call from the State Lab informing the practitioner that the specimen was unsatisfactory.

CHAPTER 3
SUMMARY OF SCREENING GUIDELINES

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3.1 Who Is Tested?

All infants born in Arizona are mandated by state law (A.R.S § 36-694) to have tests ordered to screen for specific genetic disorders.

3.2 What Are the Disorders That Are Screened For?

Arizona law specifies that the Department must establish rules for the Newborn Screening Program, including the disorders to be screened for. The types of disorders that are screened for through the program are consistent with the recommendations of the Newborn Screening Program Committee.

Most health care providers who care for infants are already very familiar with standard references to drawing blood for the "PKU test". The Department encourages practitioners to use the term "newborn screen" rather than "PKU test", because eight different screens are actually conducted, all utilizing a single blood specimen collected on a special filter paper collection device. The disorders screened for include:

1. Congenital Hypothyroidism
2. Congenital Adrenal Hyperplasia (CAH)
3. Phenylketonuria (PKU)
4. Galactosemia
5. Biotinidase Deficiency
6. Maple Syrup Urine Disease (MSUD)
7. Homocystinuria
8. Hemoglobinopathy

These disorders are due to defects that may result in severe disabilities, mental retardation, or death, if untreated. The first seven test for specific metabolic defects. The eighth, for hemoglobinopathies, tests for variations in the biochemical structure and physical properties of hemoglobin, the primary component of red blood cells.

The benefit of early screening for these disorders is that treatment in confirmed cases can be instituted as early as possible. Early detection and treatment can profoundly improve the outcome and prognosis for affected infants. Chapter 4 provides a more detailed description of the eight disorders, and important factors that impact the screening process.

3.3 When Is the Newborn Screening Test Done?

Timing for collection of the newborn screening specimen is important, because of factors that may affect the screening results. Refer to Section 5.5 for more information on these factors.

Arizona's Newborn Screening Test consists of two acceptable screens for each newborn. The Newborn Screening Program has adopted the following guidelines for when the tests are to be performed:

- The first blood specimen (first screen) should be collected from normal newborn infants as late as possible before discharge, but no later than 72 hours of age. The initial specimen should be collected prior to a blood transfusion. If the infant is sick or premature, the specimen may be delayed until 7 days of age, at the discretion of the physician (but should be collected earlier if one of the genetic disorders is suspected or if the infant may receive a transfusion).
- If the sick newborn is transported to another facility prior to 3 days of age, the receiving hospital collects the test sample.
- If the infant is to be discharged from the hospital (or attending practitioner, if the birth was not in a hospital) prior to 24 hours of age, then the test must still be performed prior to discharge.
- The second blood specimen (second screen) should be collected at one to two weeks of age, or at the time of the first outpatient visit to the baby's physician after discharge.
- If the infant is discharged prior to 24 hours of age, a second screen is required at the time of the first visit to the baby's physician.

3.4 Who Is Responsible for Ordering Newborn Screening Tests?

Practitioners who attend the infant's birth are responsible for ordering the first test, or ensuring that the pediatrician or infant's primary care provider orders the test. For most hospitals, standing nursery orders are written for collection of the newborn screening specimen at discharge or prior to 72 hours of age.

Per Arizona State Administrative Code (A.A.C. R9-14-503):

For births that occur within a hospital or other institution

"An administrator shall ensure that a first specimen is collected from each newborn born at the health care facility unless the newborn is transferred before the newborn is three days old or the newborn dies before the specimen is collected. If a newborn is admitted to a health care facility or transferred to another health care facility, the administrator of the receiving facility shall verify that the first specimen has been collected before

admission or transfer. If the administrator cannot verify that the first specimen has been collected, the administrator shall ensure that a health care provider or the health care provider's designee collects the specimen."

For births that occur outside a hospital or institution

"If a home birth is attended by a health care provider, the health care provider or health care provider's designee shall collect the first specimen for the newborn; complete the information requested on the specimen collection kit; and submit the specimen collection kit to the newborn screening laboratory within 24 hours after the specimen is collected."

Second screening tests should be collected

"After a first specimen is collected, a health care facility's designee, a health care provider, or the health care provider's designee shall collect a second specimen according to whichever of the following occurs first:

1. If a home birth attended by a health care provider, when the newborn is seven through 14 days old;
2. If a newborn is in a health care facility, when the newborn is seven through 14 days old; or
3. At the time of a newborn's first visit to a health care provider after discharge."

3.5 How Are Specimens Collected?

The preferred method for collecting blood samples is the direct application of blood drops, obtained from a lancet puncture to the newborn infant's heel, onto a special filter paper form. Techniques and tips for collecting and submitting the newborn screening blood specimens are outlined in detail in Chapter 5.

3.6 Who Is Responsible for Collecting Specimens?

Per the Arizona State Administrative Code R9-14-502 (B), "A health care facility's designee, a health care provider, or the health care provider's designee shall: collect a satisfactory specimen…"

3.7 Who Performs the Laboratory Screening Tests?

As of November 1, 1994, the State Lab, as the contracted central newborn screening laboratory, has conducted all newborn screening tests in Arizona. The State Lab conducts the first and second screening tests for all eight disorders, and repeat tests for single disorders identified as abnormal on a prior screen. This laboratory also reports results to physicians, hospital submitters, and Follow-up staff. Results are usually available 3 to 4 working days after receipt of the specimen.

3.8 Presentation of Information to Parent/Guardian Regarding Newborn Screening Tests

The Department will supply hospitals and practitioners with written information about the Newborn Screening Program upon request. Hospitals or practitioners should provide parents with this information before the test is performed. Parents should also be told, before their baby is discharged from the hospital, that a second screen is required, and that their doctor will want to collect another specimen at the infant's follow-up office visit, within one to two weeks of the baby's birth.

Brochures about the Newborn Screening Program are available. A video, in English and Spanish, is also available to help inform parents about the screening process. Both a copy of the video, as well as parent brochures, may be requested by calling the Newborn Screening Program at (602) 364-1409 or faxing a Newborn Screening Program – Order Form (see page 3-11).

3.9 Parental Refusal of Consent

The newborn screening tests are automatically ordered for all infants and performed prior to discharge from the hospital, or immediate care of the practitioner attending the birth, unless consent for the test is specifically refused. Parents/guardians may refuse consent for the newborn screening test for their infant after they have received information about the screening program and acknowledged that they understand the potential risks of refusal. Parental refusal of the newborn screening test must be clearly and prominently documented in the infant's medical record or birth record. The specimen collection kit documenting the refusal shall be submitted with a completed form to the newborn screening laboratory no later than 24 hours or the next working day after the form is completed.

3.10 First Screen

The first screen represents the first newborn screening blood specimen that is accepted by the State Lab for testing for the eight metabolic, endocrine and hemoglobin disorders on the newborn screening panel. Thus, if the first sample is improperly collected, stored, or transported, and is rejected by the State Lab as unacceptable, another sample must be collected. The entity or individual practitioner responsible for ordering and collection of the first screening specimen retains responsibility for coordination with the infant's health care provider and family to ensure that an acceptable first screen is received for testing. Refer to Section 6.3 for more information on follow-up of inadequate specimens.

The ideal time for collecting the first specimen for the Newborn Screening test is on the infant's third day of life. Unfortunately, the normal newborn length of hospital stay does

not accommodate the ideal, as an increasing number of newborn infants are now being discharged from the hospital or the care of the birth attendant prior to 24 hours of age. In order to have the greatest chance for conveniently capturing the newborn population of Arizona for the first screen, the first screening specimen must be obtained prior to discharge, or at 72 hours of age (see Section 3.3 for other qualifications).

3.11 Second Screen

A second screen is required for all babies born in Arizona. The second screen tests for the eight metabolic and endocrine disorders and hemoglobinopathies tested for on the first screen. The second screen can validate the results of the first screen. Some metabolic conditions, such as PKU, MSUD and homocystinuria, may not be detected if the blood for the first screen is taken too soon after birth and the specific product being tested for has not had time to accumulate. This may lead to a false negative on the first screen. The second screen can also detect delayed onset of a condition.

A routine second screen at the first visit to the physician after discharge assures timely additional results for disorders that may cause rapid onset of symptoms or for which there is a high false positive rate on first screens. It can reduce parental anxiety, as well as the number of babies returning to the office to follow up on an abnormal first screen. The hospital informs parents that their child's primary health care provider will order a second screen. If the baby is still in the hospital at seven to 14 days of age, the hospital should collect the second screen.

3.12 Recall Test

A recall test refers to a single screening test for a specific disorder performed by the State Lab in response to a prior abnormal screening test. It is generally ordered if there was an abnormal result on a second screen, or on a screen collected from an older baby (between one and twelve months of age) who just entered a physician's practice.

3.13 Verification of a Completed Screen

It is required that verification of a completed Newborn Screening test be done by the primary care physician of an infant less than one year of age who enters a physician's practice. This verification can be obtained through medical records, from documentation given to parents, from the Newborn Screening Program, or from a prior physician. If the physician cannot verify that a Newborn Screening test was completed, the physician must order another specimen to be collected and submitted for testing.

3.14 Who Is Responsible for Follow-Up on Unsatisfactory Specimens and Positive Screens?

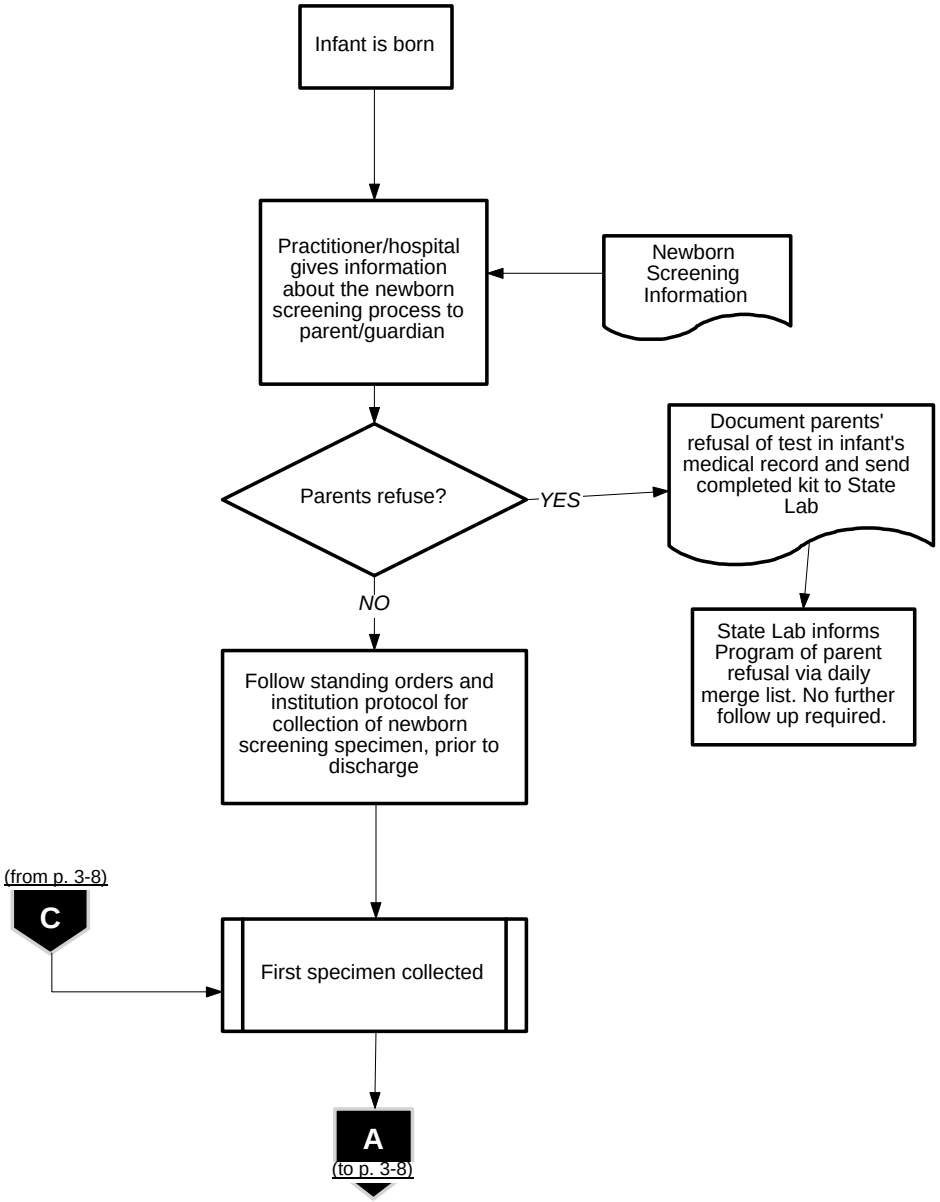
If a newborn screening test specimen is not acceptable for testing, the State Lab will notify the institution or practitioner who submitted the sample, and inform them that another sample must be collected. Notification is by telephone and in writing. The submitter of such a specimen is required to ensure that another specimen is collected and submitted as soon as possible.

For specimens having borderline or positive test results, the Department's follow-up staff will telephone the practitioner, and/or send certified letters to practitioners and parents. Practitioners are responsible for initiating timely follow-up with families to obtain another screening test and any necessary diagnostic tests, and to begin appropriate treatment. The Department's follow-up staff, submitters, and practitioners work together to locate families and assist those infants in need of immediate intervention. The Department's follow-up staff will institute emergency parent location procedures or non-compliance protocols, when necessary, to assist practitioners in locating infants with abnormal newborn screen results. These procedures may include coordination with public health agencies, social service agencies, Department of Public Safety officials, or Child Protective Services. Chapter 6 provides more information on responsibilities for reporting of results and guidelines for follow-up on inadequate specimens and abnormal results.

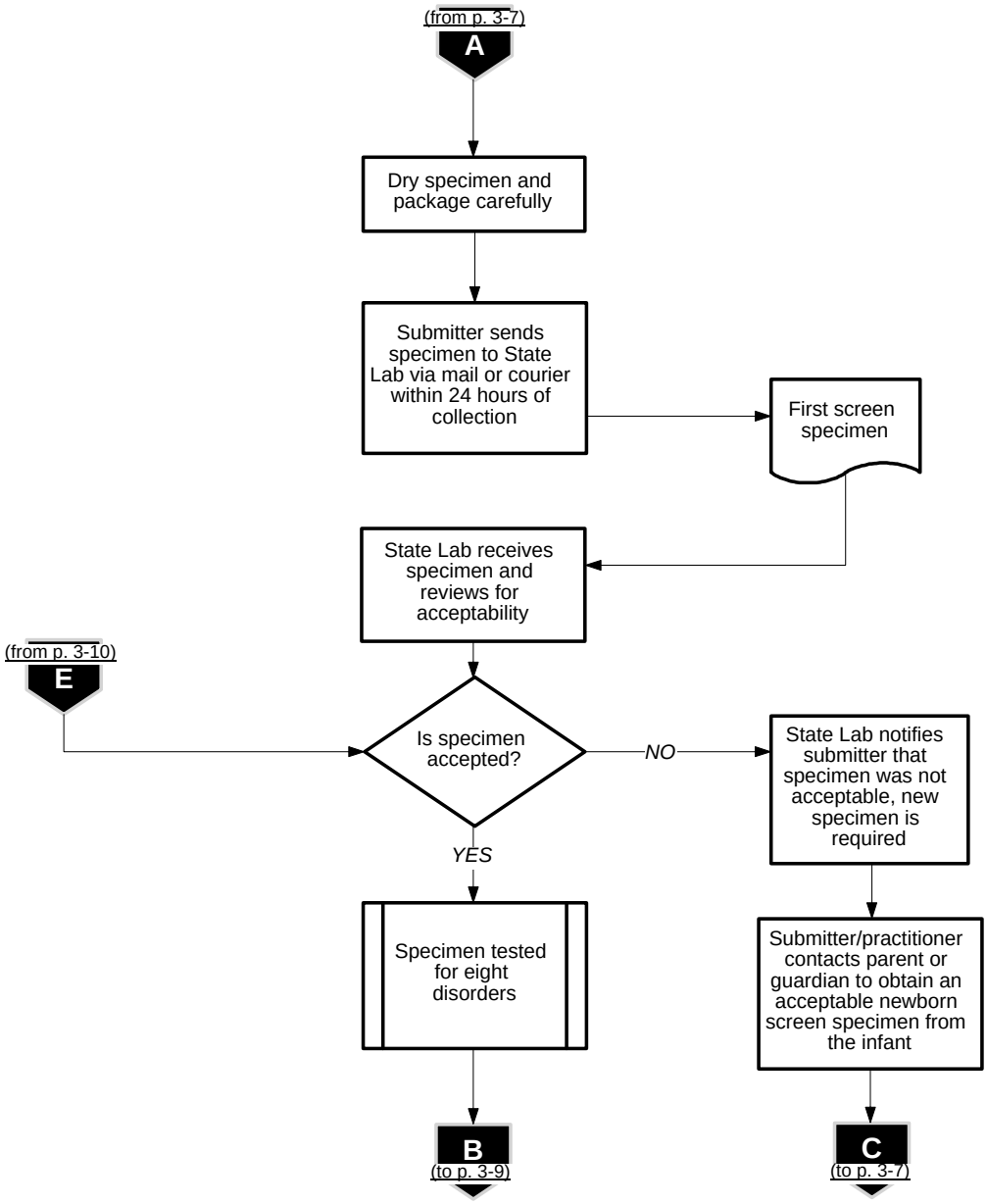
3.15 Flowchart of the Newborn Screening Process

The following pages contain a flowchart of the newborn screening process.

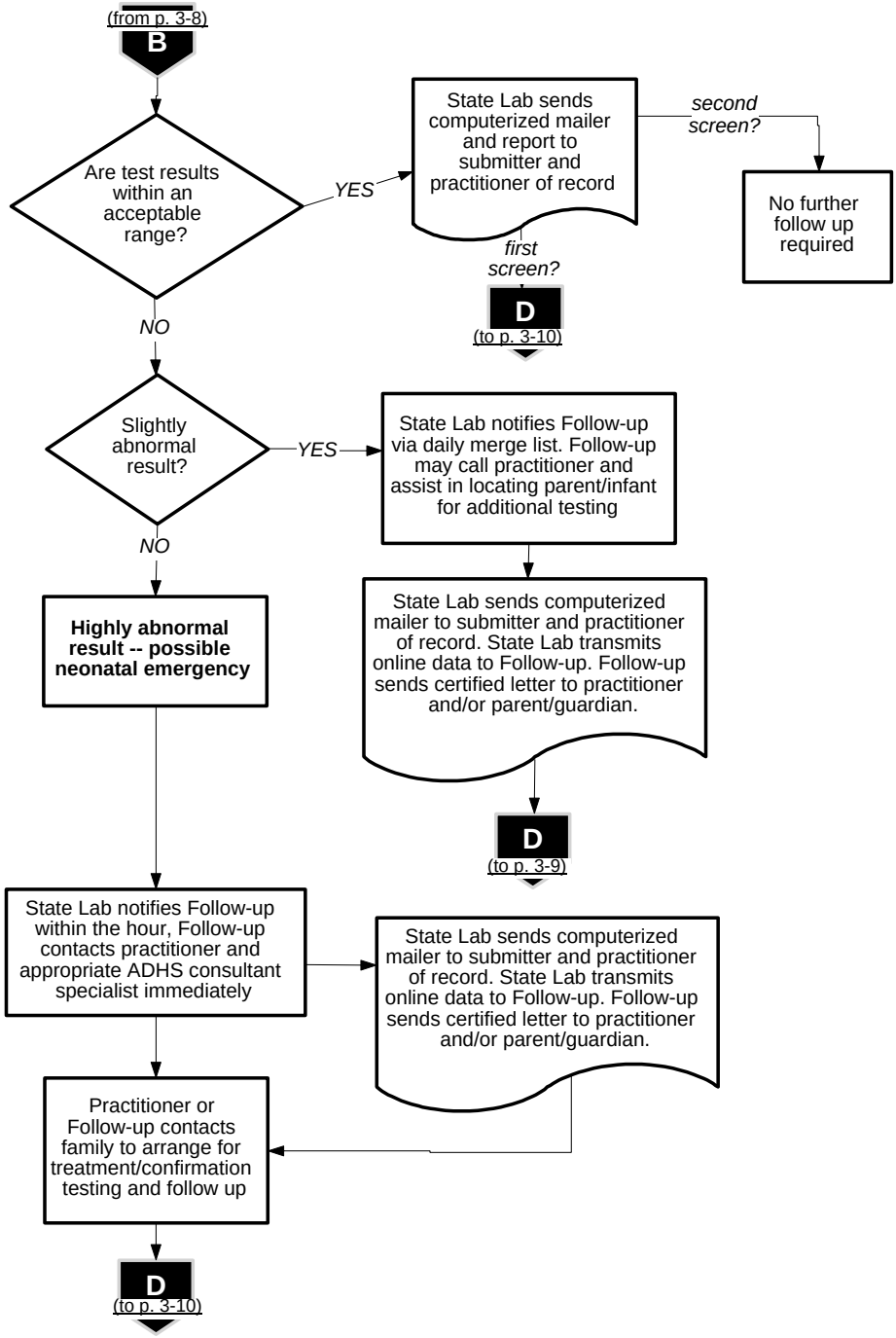
NEWBORN SCREENING PROCESS



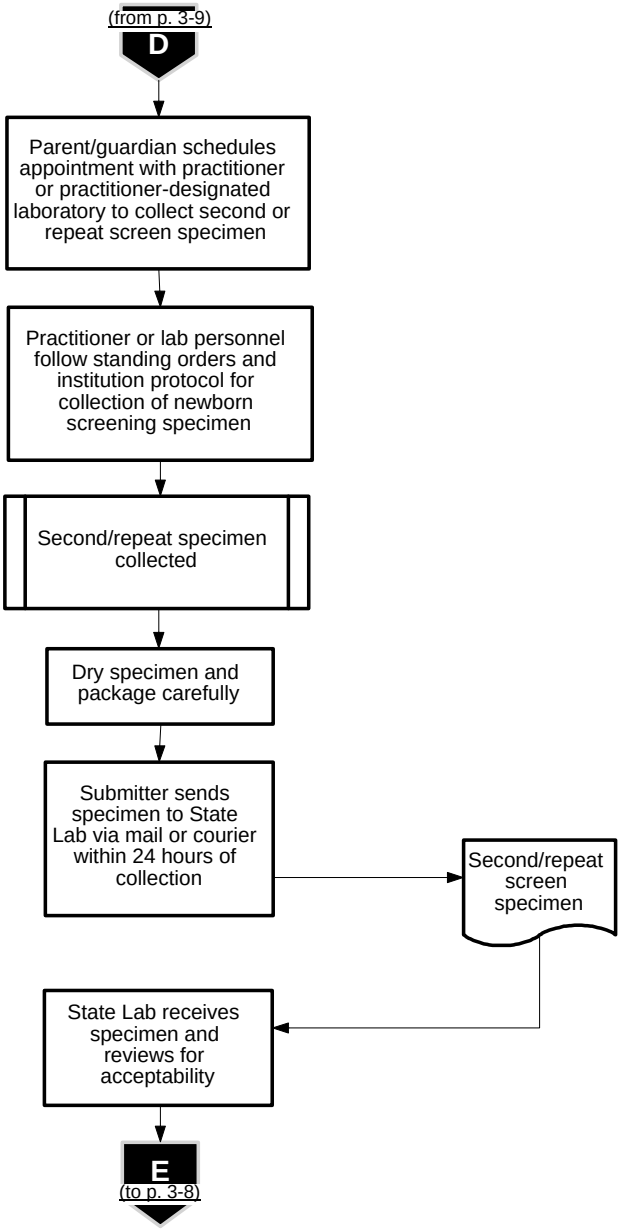
NEWBORN SCREENING PROCESS, CONTINUED



NEWBORN SCREENING PROCESS, CONTINUED



NEWBORN SCREENING PROCESS, CONTINUED



Newborn Screening Program Order Form

Please Print and Fill Out the Following Information Completely.
Incomplete Information Will Cause a Delay in Processing Your Order.

Date of Request	Requestor's Area Code & Telephone Number	Requestor's Area Code & Fax Number
Organization or Agency		
Number & Street Address		Room No./Floor
City	State	ZIP Code
Ship to the Attention of (First, Last Name)	Department	

Date Order Received @ NBS	By	Date Order Sent

Please See the Unit Quantities and Maximums and Enter Your Requirements Accordingly.

Item Number	Brochure or Item Name	No. per Unit *Maximums*	Unit	Units Ordered
NBS-01	Newborn Screening: For Your Baby's Health **(English)**	100/Pkg *Max: 10 Pkgs.*	Pkg.	
NBS-02	Newborn Screening: For Your Baby's Health **(Spanish)**	100/Pkg *Max: 10 Pkgs.*	Pkg.	
NBS-03	Newborn Screening Program **(English)**	50/Pkg *Max: 2 Pkgs.*	Pkg.	
NBS-04	Newborn Screening Program **(Spanish)**	50/Pkg *Max: 2 Pkgs.*	Pkg.	
	Newborn Screening Program Guidelines – ADHS	Each *Max: 2*	Ea.	
	Newborn Screening Practitioner's Manual – MSGN	Each *Max: 2*	Ea.	

NBHS	Your Baby's Hearing **(English)**	100/Pkg *Max: 10 Pkgs.*	Pkg.	
NBHS	Your Baby's Hearing **(Spanish)**	100/Pkg./ *Max: 10 Pkgs.*	Pkg.	
NBHS-EHDI01	Universal Newborn Hearing Screening **(English/Spanish)**	100/Pkg. *Max: 10 Pkgs.*	Pkg.	
	Newborn Hearing Screening Labels (for back of Lifetime Immunization Record)	250/Roll *Max: 10 Rolls*	Roll	
	2002 Arizona Medical Guide to Early Hearing Detection & Intervention	Each *Max: 2*	Ea.	
	Arizona Pediatric Audiology Guidelines	Each *Max. 2*	Ea.	
	Arizona Hospitals' Universal Newborn Hearing Screening Guidelines	Each *Max. 2*	Ea.	

You May Fax or Mail Your Order to the Newborn Screening Program:

FAX YOUR ORDER TO:	MAIL YOUR ORDER TO:
(602) 364-1495	Arizona Department of Health Services Attn: Newborn Screening Program 150 North 18th Avenue, Suite 320 Phoenix, AZ 85007

If You Have Any Questions, Please Call (602) 364-1409 or 1-800-548-8381 (outside Phoenix area)

Please Allow Two (2) Weeks for Your Order to be Processed and Shipped

CHAPTER 4
DESCRIPTION OF NEWBORN DISORDERS

CHAPTER 4
DESCRIPTION OF NEWBORN DISORDERS

4.1 Congenital Hypothyroidism (CH)

Causes of Congenital Hypothyroidism

Congenital hypothyroidism (CH) occurs in babies who are born without the ability to produce sufficient amounts of thyroid hormone. Thyroid hormone is important for normal function of all of the body's organs, and is essential for normal brain development. The most common causes of congenital hypothyroidism are total or partial failure of the thyroid gland to develop normally. Less commonly, hypothyroidism is induced by medications (antithyroid drugs or excess iodine) in the expectant mother, or is due to the hereditary inability to manufacture thyroid hormone. The incidence rate is 1 of every 4,000 babies born in the United States.

Clinical Features

Babies who are deficient in thyroid hormone may develop mental retardation and other signs of brain damage if this condition is not diagnosed and treated early in life. Most infants with congenital hypothyroidism appear clinically normal until about 3 months of age. Nevertheless, by this time some irreversible brain damage may have already occurred.

Signs and symptoms of CH are non-specific, but may include prolonged neonatal jaundice, constipation, lethargy and poor muscle tone, feeding problems, large tongue, puffy face, distended abdomen, and umbilical hernia.

Screening Tests for Hypothyroidism

Arizona has a two-tiered test for hypothyroidism. The initial screening test for hypothyroidism is the T4 (thyroxine) assay. This assay is a solid-phase, time-resolved fluoroimmunoassay. Testing for TSH (thyroid stimulating hormone) is the second test performed if the T4 value is in the lowest 10% of the specimens tested. The normal range for the T4 should be greater than 6 mg/dl on the first specimen and greater than 5 mg/dl on the second specimen. The normal range for TSH levels should be less than 30 UIU/ml on the first specimen and less than 20 UIU/ml on the second specimen. A borderline abnormal result occurs when the T4 is less than or equal to 6 mg/dl with a normal TSH, or there is a slight TSH elevation regardless of T4 value. Abnormal results for hypothyroidism include a low T4 (less than or equal to 6 mg/dl) or normal T4 in conjunction with a high TSH level (greater than or equal to 60 mg/dl).

When screening tests are borderline abnormal on a first screen, the infant's physician is notified by phone and requested to collect a second newborn screening test as soon as possible. The tests recommended by the Newborn Screening Program's staff during phone conversations or in letters are per instructions from the Program's consulting pediatric endocrinologists. For an abnormal result, physicians are requested to order a blood sample for a serum thyroid panel to confirm the abnormal screening results. In the case where the T4 is low and the TSH is abnormal, consultation with an endocrinology specialist is recommended. The specialist may advise that treatment be started as soon as the serum is obtained, pending final confirmation. If the hormone levels remain abnormal, further diagnostic studies, such as thyroid scan and bone age X-rays, may be desirable to determine the type, age of onset and severity of hypothyroidism.

In premature infants, there appears to be a physiological reduction in T4 blood levels. Although common, these cases will need special follow-up to ensure that the low T4 levels rise to the proper levels as the infant matures, as will occur in all normal cases.

Treatment

Treatment of congenital hypothyroidism is simple and effective. Thyroid hormone in pill form is prescribed on a daily basis. It is crushed, mixed with food, and administered once daily. Endocrinology consultation should be obtained to determine recommendations for follow-up. Infants and children should undergo periodic developmental evaluation.

Screening Practice Considerations

Congenital hypothyroidism is one of the most common disorders detected by newborn screening. Detection does not depend on protein or lactose ingestion. The majority of infants with congenital hypothyroidism are detected on the first specimen, even if it is collected a few hours after birth. As with other screening tests, if the infant has clinical symptoms to suggest the presence of disease, further evaluation should be performed regardless of the results of the newborn screen.

The second newborn screen is required for all babies. A second screen validates the first screen and ensures that infants diagnosed with a disorder receive timely and appropriate treatment. The Academy of Pediatrics data show that 6 to 12% of infants diagnosed with congenital hypothyroidism are normal on the first screen and abnormal on the second screen. Of the babies in Arizona diagnosed with congenital hypothyroidism in 2001 and 2002, about 13.5% were normal on the first screen and abnormal on the second.

As a special note, if the specimen is collected within the first three hours of life, the TSH may be markedly elevated, due to cooling of the infant in the extrauterine environment, leading to a false positive result. A blood transfusion may also alter the T4/TSH values.

4.2 Phenylketonuria (PKU)

Causes of Phenylketonuria

Phenylketonuria is an autosomal, recessively inherited metabolic disorder, caused by an enzymatic defect such that the body cannot process the amino acid phenylalanine properly. All other metabolic processes are intact, but phenylalanine, which is a component of all dietary protein, accumulates in the blood. This is due to a lack of phenylalanine hydroxylase activity, the enzyme that catalyzes the conversion of phenylalanine to tyrosine. The incidence rate is 1 in every 15,000 babies born in the United States.

Clinical Features

PKU can be adequately treated if dietary restriction of phenylalanine is begun within the first 4 weeks of life. When untreated, infants develop symptoms of brain damage and mental retardation that become evident between 6 and 12 months of age. A "mousy" odor of sweat and urine is noticed frequently in older individuals, but may not occur before one month of age.

Overall, PKU occurs most frequently in infants of Caucasian ethnicity and is less common in other races. Although severe mental deficiency is the rule in untreated cases, occasionally, affected adults are found with normal or near normal intelligence.

Maternal PKU

Maternal PKU is the result of high blood levels of phenylalanine in the mother with PKU during her pregnancy. The elevated levels of phenylalanine in the maternal blood crosses the placenta, resulting in elevated fetal blood levels, mimicking the effects of PKU in a genetically normal infant. This is a disorder that may result in inaccurate results with early testing, because the newborn will be reflecting the mother's phenylalanine levels. If the newborn has two subsequent normal screens but has growth retardation, microcephaly, or malformations, there is the possibility that the mother had maternal PKU. If this occurs, it is important that the mother receive appropriate testing and counseling to help prevent these types of outcomes with future offspring.

Variant Forms of PKU (Hyperphenylalaninemia)

There are several intermediate forms of hyperphenylalaninemia in which the plasma phenylalanine (phe) levels are lower than in classic PKU but are higher than the levels in the general population. In these cases, mental retardation may occur, but usually in the milder variants does not appear. Blood levels may remain high throughout life or may

gradually fall toward normal. Treatment is dependent on blood levels. Even in mild cases, there seems to be an increased risk of the maternal PKU syndrome.

Recently, new forms of hyperphenylalaninemia caused by defects of tetrahydrobiopterin (THB) synthesis have been recognized. These children have progressive neurological damage with seizures and steady deterioration, which becomes noticeable between 2 and 20 months of age, despite early treatment with a low phenylalanine diet. In view of the severity of this group of diseases, all infants with persistently abnormal levels of phenylalanine should be tested by special blood and urine tests for abnormalities indicative of a THB synthesis defect.

Screening Test for PKU

PKU is tested for using a fluorometric assay to detect elevated levels of phenylalanine. A plasma phenylalanine level from 2.1 mg/dl to 2.9 mg/dl is reported as borderline. These levels are higher than those found in the general population, but do not meet the test manufacturer's criteria for an abnormal test. A phenylalanine equal to or greater than 3.0 mg/dl is abnormal. In both cases, prompt further testing is critical. Consultation with a metabolic geneticist is recommended. Depending on the numerical value of the test result, another screening test or a serum level of phenylalanine and tyrosine may be recommended.

Treatment

With early and proper treatment, mental retardation is totally preventable. Treatment should be started as soon as possible after birth in any infant with an elevated phenylalanine level, and should be continued indefinitely. Because phenylalanine is an essential amino acid, it cannot be totally omitted from the diet. Frequent monitoring and diet adjustment are necessary to prevent critical nutritional inadequacies, or elevated phenylalanine levels.

If treatment is not started for some weeks, the results are more variable and the IQ of the child tends to be lower. Persons who are not treated until after 6 months of age may show some improvement in IQ, although they are likely to remain retarded. Patients who are not started on treatment until they are older usually show little change in IQ, but a low phenylalanine diet may help to control serious behavioral problems. Treatment is recommended throughout life. Careful monitoring of female patients is critical to avoid the effects of maternal PKU.

Screening Practice Considerations

Detection of increased levels of phenylalanine in the blood may depend on the amount of protein (formula or milk feedings) ingested by the infant. If an infant is tested "early" (at

less than 48 hours of age), insufficient amounts of phenylalanine may have accumulated, leading to a false negative result. The routine second newborn screening test should provide a valid result.

4.3 Galactosemia

Causes of Galactosemia

Galactosemia is an autosomal, recessively inherited metabolic disorder. This disorder is the result of elevated blood galactose levels due to a deficiency in one of three enzymes in the galactose catabolic pathway. The three enzymes are galactose-1-phosphate uridyl-transferase (GALT; also referred to as Gal-1-PUT), galactokinase, and UDP-galactose-4-epimerase. Newborn screening detects classic galactosemia, the most severe form of galactosemia, which is caused by a deficiency of Gal-1-PUT. The main dietary source of galactose is as a component of the disaccharide lactose, the principal carbohydrate component of mammalian milk and most non-soy commercial infant formulas. Lactose is hydrolyzed to glucose and galactose in the intestine. The incidence rate for galactosemia is 1 in every 60,000 babies in the United States.

Clinical Features

The early clinical features of classic galactosemia include neonatal hypoglycemia, liver damage, jaundice, failure to thrive, lethargy, and sepsis. Death may result from gram-negative sepsis within one to two weeks after birth. If the infant survives the neonatal period and the disorder is not detected, cataracts, cirrhosis, Fanconi's Syndrome, and mental retardation develop.

There are several genetic variants of the disease. These are characterized by less severe reductions in enzyme activity. Most of these cases are asymptomatic and are detected because of a persistent abnormality in enzyme activity. However, some of these cases may require dietary therapy if there are symptoms indicative of galactose toxicity. For this reason, many of these infants require further testing, and should be evaluated by the follow-up team at a metabolic center or clinic.

Screening Tests for Galactosemia

Classic galactosemia is detected utilizing the GALT fluorometric screen. This test is a semi-quantitative or quantitative assay of galactose-1-phosphate-uridyl-transferase activity. The test results are expressed in fluorescence or enzyme activity units. A test result of 2.4 U/g Hb or less is considered to be abnormal. Variant forms of the disorder will result in reduced, but not absent activity. Little to no fluorescence detected indicates a highly abnormal result, and a possible neonatal emergency.

Treatment

The galactosemia syndromes are treated by rigid dietary exclusion of all galactose. This galactose-free diet requires close nutritional supervision. The patient will require medical care to manage those symptoms that are not prevented by diet.

Screening Practice Considerations

Detection of this disorder does not depend on the timing of collection or type of feeding, because it is an enzyme assay. The GALT test on the first specimen should be abnormal in all severe (classic) galactosemic infants, unless the infant has had a transfusion. Because the assay tests for enzyme activity in red blood cells, false negatives can result after a blood transfusion, so it is important to obtain a specimen before a transfusion. The enzyme is prone to damage if the sample is delayed in the mail or exposed to high temperatures. If the sample is heat damaged, a false positive result may occur.

Galactose accumulation depends on lactose ingestion, so blood galactose is normal in galactosemic infants receiving soy-based formula or other non-lactose containing forms of nutrition. If galactosemia is a consideration, galactose should be restricted until an accurate test has been obtained. Since the GALT test is not affected by the formula given to the infant, it is recommended that galactose-free formula be given immediately. **Galactosemia is a medical emergency and it should be considered in any infant with non-glucose reducing substances in the urine and signs and symptoms consistent with the disorder.**

4.4 Homocystinuria

Causes of Homocystinuria

Homocystinuria is an autosomal, recessively inherited disorder of methionine metabolism. This disorder is characterized by the elevations of both homocystine and methionine in blood and urine. It is caused by defective activity of the enzyme cystathionine ß−synthetase. About 1 in 5,000 infants is found to have elevated methionine in routine testing. In most instances, this is a benign, temporary abnormality due to immature enzyme levels or a high protein intake. The incidence of homocystinuria is 1 in 100,000 infants born in the United States.

Clinical Features

There are no symptoms of homocystinuria in the newborn period. However, without treatment these children develop seizures, osteoporosis, dislocated lenses, liver damage, connective tissue damage, and arterial thrombosis. Many children have mental

deficiencies, and many have emotional problems. Heterozygotes (carriers) may be at risk of thromboembolic disease.

Screening Tests for Homocystinuria

A bacterial inhibition assay for methionine (Guthrie test) is used for screening. Normal methionine levels should be less than 2 mg/dl. Consultation with a metabolic geneticist is recommended. Depending on the numerical value of the test result, another screening test or a serum level of methionine, homocystine or other compounds may be recommended.

Treatment

Some individuals respond to high doses of vitamin B6 (pyridoxine, 250-500 mg daily). Other individuals need a diet restricted in methionine. Other necessary amino acids, vitamins, and minerals are provided by a special metabolic food. Because methionine is an essential amino acid and cannot be totally excluded from the diet, regular dietary monitoring is necessary. Thromboembolic events may be prevented by antiplatelet agents, such as aspirin or dipyrimazole. The outcome for treated individuals is good.

Screening Practice Considerations

Detection of increased levels of methionine in the blood depends on protein intake and metabolism. If an infant is tested "early" (less than 48 hours of age), insufficient amounts of methionine may have accumulated, leading to a false negative result. A routine second newborn screening test should provide valid results since the infant would have had several feedings by that time.

Since testing is performed by a bacterial inhibition assay, administration of antibiotics to an infant before a specimen is collected may lead to an inconclusive result for homocystinuria.

4.5 Maple Syrup Urine Disease (MSUD)

Causes of Maple Syrup Urine Disease

Maple Syrup Urine Disease (MSUD) is an autosomal, recessively inherited disorder, characterized by the inability of the body to metabolize the branched-chain amino acids, leucine, isoleucine, and valine, due to deficient activity of branched-chain α-ketoacid dehydrogenase. The severity of the disorder may vary. The incidence rate is 1 in every 200,000 infants born in the United States.

Clinical Features

MSUD is a rare disorder associated with progressive neurological damage. In the classic form of MSUD, the symptoms begin shortly after birth with the intake of dietary protein. The catabolism of the excess branched-chain amino acids and ketoacids is blocked, which results in their accumulation in the blood. The excess amino acids and ketoacids are excreted in the urine. Symptoms generally include poor feeding, irritability, vomiting, and central nervous system depression. Without treatment, the infant becomes progressively worse, and coma and death generally occur within 2 to 4 weeks.

Biochemically, in MSUD, there is metabolic acidosis and, often, hypoglycemia. Plasma leucine starts to rise usually within 24 hours of birth, and within a few days ketoacids appear in the urine. These ketoacids have a characteristic sweet maple syrup odor, which gives the disease its name. As with most hereditary disorders, there are less severe variants, the mildest of which may go undetected for some months until tests for an unexplained illness uncovers the disorder.

Screening Tests for MSUD

MSUD is detected by testing for abnormal levels of the amino acid leucine, utilizing the Guthrie test (a bacterial inhibition assay). Normal leucine levels are less than 4 mg/dl. Levels equal to or greater than 4 mg/dl represent a highly abnormal result, and a potential neonatal emergency.

Treatment

Any baby in whom the plasma leucine is 4 mg or greater should be considered to have MSUD until proven otherwise. Any infant with this disorder needs to be transferred to a major medical center as quickly as possible because the investigations and management are very complicated, and death can occur rapidly in untreated cases. Treatment, which must be continued for life, is with a protein-restricted diet that limits the intake of branched-chain amino acids. Early diagnosis, appropriate intervention and long-term management can help improve neurologic development.

Screening Practice Considerations

Detection generally depends on protein ingestion. An affected infant must be detected early if life-threatening problems are to be prevented, but specimens collected prior to 48 hours of life may result in inadequate levels of excess amino acids for detection by newborn screening. Because testing is performed by a bacterial inhibition assay, administration of antibiotics to an infant before a specimen is collected may lead to an inconclusive result for MSUD.

4.6 Biotinidase Deficiency

Causes of Biotinidase Deficiency

Biotinidase is an enzyme that liberates biotin, an essential cofactor, from a bound form so that it can be used by the body. Abnormal biotin metabolism, caused by defective biotinidase activity, results in improper functioning of several other enzyme systems, leading to irreversible neurological damage. This disorder is an autosomal recessively inherited disorder. The incidence rate is 1 in 60,000 infants born in the United States.

Clinical Features

The symptoms of biotinidase deficiency are variable with respect to age of onset, frequency and severity. Symptoms generally appear in infancy and may include seizures, skin rash, hair loss, hypotonia, ataxia, hearing loss, optic nerve atrophy, developmental delay, and metabolic acidosis that can result in coma and death.

Screening Tests for Biotinidase Deficiency

Detection of enzyme activity is through a qualitative colorimetric assay. In the presence of the enzyme, a color change occurs. An abnormal result would occur if the sample did not undergo a color change. If the color change in the sample were not equal to the color change in the control (pale), a borderline abnormal result would be reported.

Treatment

The acute symptoms of biotinidase deficiency will completely disappear by giving affected children pharmacological doses of biotin, usually 10 mg per day. If given early enough in the infant's life, the prognosis for normal growth and development is good. If children are not detected until irreversible neurological damage has occurred, treatment with biotin will prevent further damage, but not reverse the damage already done.

Screening Practice Considerations

Detection of the deficiency does not depend on the timing of collection or type of feeding, because it is an enzyme assay. This disorder should therefore be detected on the first specimen unless the infant has had a transfusion, so it is important to obtain a specimen before a transfusion. The enzyme is prone to damage if the sample is delayed in the mail or exposed to high temperatures.

4.7 Congenital Adrenal Hyperplasia (CAH)

Causes of Congenital Adrenal Hyperplasia

Congenital Adrenal Hyperplasia (CAH) is an autosomal, recessively inherited, metabolic disorder, characterized by the inability to synthesize cortisol. The major cause of CAH is 21-hydroxylase (21-OHase) deficiency. When the 21-OHase enzyme is deficient, a block occurs in the production pathways for both cortisol and usually aldosterone, and the adrenal gland is unable to produce adequate amounts of these two hormones.

The products that are made through the steps preceding the block accumulate and are used by other unblocked pathways, especially the one for the production of male sex hormones. As a result, the adrenal glands produce abnormally high amounts of androgens, which are released into the bloodstream. These increased levels of androgens are not known to affect the growing male fetus; however, they do cause abnormal development of the external sex organs of the growing female fetus. This can include enlargement of the clitoris and/or abnormal fusion of the labial structure, and can be severe enough to result in incorrect gender assignment of virilized females as males.

Clinical Features

There are three forms of CAH: salt-wasting, simple virilizing, and non-classical. The Arizona Newborn Screening Program screens for the salt-wasting and simple virilizing forms of CAH. Left untreated, the results of CAH may include ambiguous female genitalia, excess virilization, rapid growth with accelerated skeletal maturation, short stature, salt-losing syndrome and possible death. In the salt-wasting form an infant can have an adrenal crisis within the first 5 days to the first few months of life. Most infants will have an adrenal crisis within the first 10 days of life. CAH occurs in 1 in 15,000 infants.

Screening Tests for Congenital Adrenal Hyperplasia

Infants are tested through a solid phase, time-resolved fluoroimmunoassay for elevated levels of 17α-OH-progesterone (17-OHP). The infant's weight is used as an indicator of its gestational age, and test results are weight adjusted to determine whether results are normal or abnormal for CAH. As a result, the levels of 17-OHP considered normal and abnormal vary between very low birth weight, low birth weight, and normal birth weight infants. It is important that accurate weights (preferably in grams) be provided for infants being screened for CAH. It is important to keep in mind that sick and premature infants may have elevated levels of 17-OHP because the stress of illness stimulates adrenal steroid production and an immature adrenal gland sustains increased plasma concentrations of most adrenal metabolites.

Treatment

Treatment of congenital adrenal hyperplasia depends on the type of CAH affecting the infant. Cortisol replacement is used for both the salt wasting and the simple virilizing forms. Mineral corticoid treatment supplementation is added for the salt wasting form of CAH. Surgery can be done to correct ambiguous female genitalia. Early detection and treatment can be life saving, and result in a decreased risk of a serious salt-losing crisis and earlier correct gender assignment of virilized girls. Appropriate and early treatment will contribute to normalization of growth and final height, and timely puberty.

Screening Practice Considerations

The need for accurate data on the specimen collection form is always important, but in the case of CAH, accurate information is crucial. The interpretation of screening results is based on infant weight as an indicator of gestational age, with the cut-offs adjusted for weight. Inaccurate or missing data will increase the number of false positive results. If this information is missing, the laboratory will use the most conservative cut-off to ensure that an affected infant is not missed.

4.8 Hemoglobinopathy

Causes of Hemoglobinopathy

Most clinically significant hemoglobinopathies are inherited defects of the β-globin chain of adult hemoglobin. Red blood cells of newborns have a predominance of fetal hemoglobin, which does not contain β-globin. For this reason, signs and symptoms of β-globin abnormalities are usually not apparent at birth, but become evident at 4 to 6 months of age after adult hemoglobin replaces fetal hemoglobin.

Most of the hemoglobinopathies detected by newborn screening are the result of single amino acid substitutions in the globin chain and are inherited as autosomal recessive disorders. Persons with two abnormal globin genes (homozygotes or double heterozygotes) have a disease. Individuals with one abnormal globin gene (heterozygotes) are said to have a hemoglobin trait and are carriers of the disease. Thalassemias are caused by decreased synthesis of the globin chains. Thalassemia genes in conjunction with genes for globin variants may produce serious hemoglobinopathies.

The frequency of a hemoglobinopathy varies among ethnic groups. Sickle hemoglobin is found in descendants of people from Africa, Italy, Greece, Turkey, Arabia, and India. In the U.S., sickle hemoglobin is encountered in Whites and Hispanics, as well as African Americans. Hemoglobin C occurs in descendants of people from central and western Africa. Hemoglobin E is common in persons of Southeast Asian ancestry. Thalassemia genes originated in Italy, Greece, Asia and Africa.

Clinical Features

Sickle cell disease occurs in persons homozygous for the sickle gene (sickle cell anemia), doubly heterozygous for sickle hemoglobin and β-thalassemia (sickle β-thalassemia) or doubly heterozygous for sickle hemoglobin and hemoglobin C (SC Disease). Persons who inherit hemoglobin S with hemoglobin D or O also have a sickling disease. Infants with sickle cell disease may present with dactylitis (inflammation of fingers and toes), fever, sepsis, jaundice, anemia, or splenic sequestration (which may be life threatening in a child), at any time after the age of 3 to 6 months. Some of the symptoms occur as the disease progresses. These disorders are heterogeneous in severity, and some clinical features are not present in all affected individuals.

In other hemoglobin diseases, the type of hemoglobin variant influences clinical features. Homozygous hemoglobin C or hemoglobin E disease show only mild hemolytic anemia. Persons with thalassemias have microcytic, hypochromic anemia and the severe forms have hemolysis, and may be transfusion dependent. Most hemoglobin traits are associated with few or no clinical problems. The value of trait detection is the opportunity to educate families, to test other family members, and to provide genetic counseling.

Screening Tests for Hemoglobinopathy

The primary screening method is performed by isoelectric focusing (IEF). Abnormal screens are analyzed again by high performance liquid chromatography (HPLC) or Isoscan gels. Screening detects the presence of abnormal hemoglobin, which can be specified during the HPLC testing.

Treatment

Treatment for sickling diseases includes the following:

1. Genetic counseling and education for parents;
2. Overall medical management, planned in consultation with a comprehensive sickle cell center or a pediatric hematologist;
3. Penicillin prophylaxis started by three months of age for children with sickle cell anemia;
4. Prompt medical evaluation, including appropriate cultures and parenteral antibiotics for all significant febrile illnesses ($>101^0$ F);
5. Prompt medical evaluation for signs and symptoms of splenic sequestration;
6. Pneumococcal vaccine at 2 years of age;
7. Other treatments, including transfusion, based on clinical course.

Screening Practice Considerations

The primary purpose of hemoglobinopathy screening is the identification of infants with sickle cell diseases. Early intervention has been shown to markedly reduce morbidity and mortality. Blood transfusions may cause false negative results; therefore specimens should **always** be collected prior to a blood transfusion. If a blood transfusion does occur before a specimen is collected, a repeat hemoglobin electrophoresis should be obtained 3 to 4 months after the date of the last transfusion.

4.9 Summary of Disorders Screened in the Newborn Screening Program

CONDITION	ANALYTE TESTED FOR	INCIDENCE	SYMPTOMS IF NOT TREATED	TREATMENT
Hypothyroidism	T4 with TSH confirmation	1 : 4,000	Mental retardation, other brain damage, growth delay	Thyroid hormone (L-thyroxine)
Hyperphenylalaninemia (including PKU)	Phenylalanine	1 : 15,000	Severe mental retardation, seizures	Low phenylalanine diet
Biotinidase Deficiency	Biotinidase	1 : 60,000	Mental retardation, deafness, seizures, skin rash, alopecia	Biotin
Galactosemia	GAL-1-PUT	1 : 60,000	Severe brain damage, kidney damage, and cataracts in neonates; death if untreated	Galactose-free diet
Maple Syrup Urine Disease	Leucine	1 : 200,000	Neonatal coma, convulsions, mental retardation, acidosis; death if untreated	Diet low in branched-chain amino acids
Homocystinuria	Methionine	1 : 100,000	Mental retardation, bone damage, thrombosis, osteoporosis, dislocated lenses, weakness of the aorta, liver damage	Vitamin B6 if responsive, and/or diet low in methionine
Congenital Adrenal Hyperplasia (CAH)	17-hydroxyprogesterone	1 : 15,000 (salt wasting and simple virilizing)	Salt wasting syndrome, ambiguous female genitalia, excess virilization, rapid growth, accelerated skeletal maturation, short stature, death.	Cortisol replacement, mineral corticoid, salt supplementation, and surgery
Hemoglobinopathies (including sickle cell disease)	Hemoglobin	Sickle cell disease-many variations of illness 1 : 375 in African-Americans	For sickle cell disease, lifelong hemolytic anemia and a variety of complications secondary to increased propensity to infection and vaso-occlusive episodes	Early comprehensive care and prophylactic penicillin reduce morbidity and mortality in sickle cell anemia.

4.10 Chart of Arizona Newborn Screening Program Test Values and Standards

CONDITION	TEST ANALYSIS	NORMAL RANGE	BORDERLINE RESULT	ABNORMAL RESULT
Hypothyroidism	**T4** with **TSH** confirmation (time-resolved fluorescence)	**1st screen –** **T4** > 6 mg/dl **TSH** < 30 UIU/ml **2nd Screen –** **T4** > 5 mg/dl **TSH** < 20 UIU/ml **TSH** is tested if value of T4 is in the lowest 10% of the samples tested	**1st Screen –** **T4** ≤ 6mg/dl with **TSH** normal (< 30 UIU/ml) or slightly elevated (30 to 59.9 UIU/ml) **or TSH** slightly elevated (30 to 59.9 UIU/ml) with any **T4** value **2nd Screen –** **T4** ≤ 5mg/dl with **TSH** normal (< 20 UIU/ml) or slightly elevated (20 to 59.9 UIU/ml) **or TSH** slightly elevated (20 to 59.9 UIU/ml) with any **T4** value	**TSH** ≥ 60 UIU/ml on either screen
Hyperphenylalaninemia (including PKU)	Perkin Elmer Neonatal Phenylalanine Test Kit (fluorometric assay)	< 2.1 mg/dl	2.1 – 2.9 mg/dl	≥ 3 mg/dl
Biotinidase Deficiency	Biotinidase (colorimetric assay)	Color change equivalent to control	Color change less than control (pale)	No color change
Galactosemia	GALT fluorometric screen	> 2.4 U/g Hb	------N/A----	≤ 2.4 U /g Hb
Maple Syrup Urine Disease	Guthrie test Bacterial inhibition assay (BIA)	< 4 mg/dl	-----N/A-----	≥ 4 mg/dl
Homocystinuria	Guthrie test Bacterial inhibition assay (BIA)	< 2 mg/dl	-----N/A-----	≥ 2 mg/dl
Hemoglobinopathies (including sickle cell disease)	Hemoglobin IEF, HPLC, Isoscan	Normal Hb present	-----N/A-----	Abnormal Hb present at > 1%
Congenital Adrenal Hyperplasia (See 4.11)	Auto Delfia Perkin Elmer (time-resolved fluorescence); 17 – hydroxyprogesterone (17-OHP) assay	See **4.11**	See **4.11**	See **4.11**

4.11 Value Ranges for Congenital Adrenal Hyperplasia (CAH) Results

Birthweight Range	Normal Range	Borderline Result	Abnormal Result
Above 2249 g	< 50 ng/ml	50 - 89.9 ng/ml	≥ 90 ng/ml
From 1751 - 2249 g	< 65 ng/ml	65 - 89.9 ng/ml	≥ 90 ng/ml
From 1251 - 1750 g	< 90 ng/ml	90 - 134.9 ng/ml	≥ 135 ng/ml
Below 1251 g	< 135 ng/ml	135 - 159.9 ng/ml	≥ 160 ng/ml

CHAPTER 5
SPECIMEN COLLECTION AND SUBMITTAL

CHAPTER 5
SPECIMEN COLLECTION AND SUBMITTAL

5.1 Introduction

This chapter outlines important information and guidelines for properly collecting newborn screening specimens and submitting them to the Arizona State Lab (State Lab). The Department has contracted with the State Lab to conduct testing for the Newborn Screening Program. On both the first and second newborn screening specimens, Arizona conducts tests for eight disorders from each blood specimen. The specimen is collected by direct application of blood drops from the infant's heel onto the filter paper of a special form. This form is called the Newborn Screening Specimen Collection Kit.

Many factors can influence the quality of the specimen, or the quantitative results of the test, including, but not limited to: timing of the collection of the specimen; medications; therapies; administration of blood products; ingestion of protein; source of blood utilized; techniques used to obtain the specimen; and procedures for handling screening forms once the blood samples are collected. These factors are discussed in Section 5.5.

The Department promotes adherence to the standard collection technique documented in the National Committee for Clinical Laboratory Standards' (NCCLS) approved standard LA4-A2, Vol 12, No 13, "Blood Collection on Filter Paper for Neonatal Screening Programs." Page 5-16 contains a chart prepared by the NCCLS that provides step-by-step illustrations of the blood collection process.

Permission to use portions of LA4-AS, "Blood Collection on Filter Paper for Neonatal Screening Programs - Second Edition; Approved Standard," has been granted by NCCLS. The complete current standard may be obtained from NCCLS, 940 West Valley Road, Suite 1400, Wayne, PA 19087.

5.2 Obtaining an Identification Code

Each entity that sends specimens to the State Lab or receives test results from the State Lab must have a unique Identification Code. This code is designated and assigned by the State Lab, and must appear on <u>each</u> newborn screening specimen collection kit submitted to the State Lab. If you or your organization already has an Identification Code for newborn screening, you may continue to use that same identification code.

If you need to obtain an Identification Code, you may call the State Lab's Newborn Screening Data Entry Section at (602) 542-1187. You will need to provide complete address and contact information, as well as telephone and fax numbers.

5.3 Obtaining Newborn Screening Specimen Collection Kits

Newborn Screening Specimen Collection Kits are special forms for collecting blood specimens, and may be obtained directly from the State Lab. The kits are provided to any potential submitter free of charge. Submitters and insurance companies will only be charged for the forms submitted that contain blood samples satisfactory for testing, and will be billed for completed tests on a monthly basis.

ALERT! The regulatory changes in shipping of dried blood spots, including the necessity of double packaging and the use of a biohazard symbol (sticker or printed) on the dried blood spot card, have been finalized. These United States Postal Service Domestic Mail Manual revisions are effective June 12, 2003. The flap covering the dried blood spots on the specimen collection kit and the mailing envelope count as double packaging. In the future, Arizona's kits will have the biohazard symbol pre-printed on the flap. Currently, you will be receiving small biohazard labels with your orders of kits. Please place the biohazard labels on the top of the flap portion of the specimen collection kit.

You may telephone the State Lab's Receiving Unit at (602) 542-1190 to order these specimen collection kits. The kits may also be obtained by completing and mailing the order form found at the end of this chapter (page 5-17).

5.4 Completion of Required Information on Specimen Collection Kits

It is critical that the Newborn Screening form portion of the specimen collection kit be filled out completely and accurately. The forms have been revised as of July 2, 2002, and there have been some changes in the information requested. The information requested on the form is an important aid in interpreting test results and determining proper follow-up procedures. Information about the infant, mother and physician is critical for rapid follow-up of suspicious or abnormal results. The time and date the specimen was collected, the infant's date of birth, an AHCCCS number (if applicable), and the mother's date of birth, maiden name and social security number are also important.

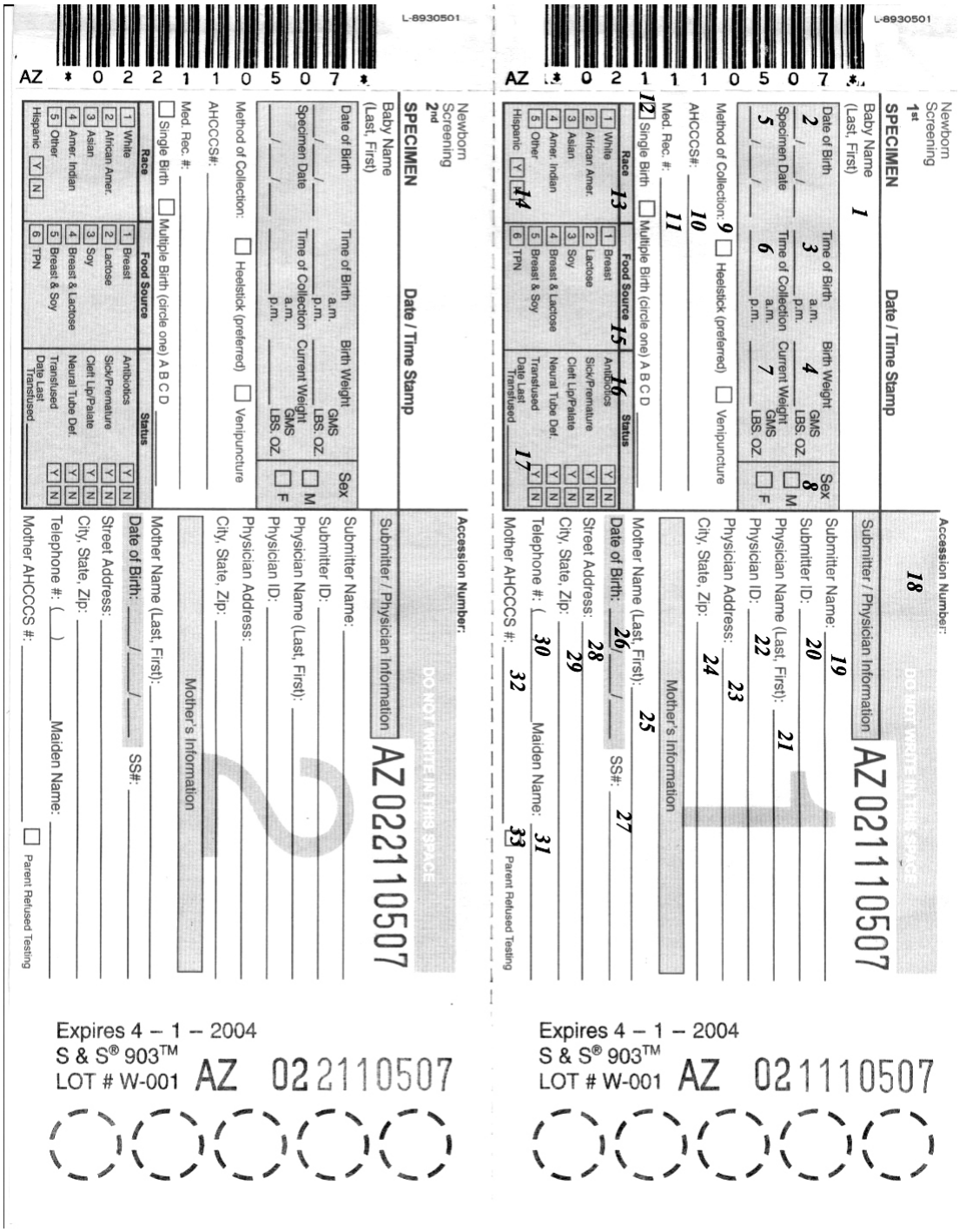
As of January 1, 2003, the State Lab needs to collect complete insurance information for second screens sent by other than a hospital submitter. When a physician's office or a non-hospital laboratory sends in a second screen, they need to provide a copy, front and back, of the patient's/parent's insurance card or place a sticker with this information on the back of the top sheet of the form portion of the specimen collection kit. This information is vital for the billing process and must be received with the specimens. If this information is not received, staff from the State Lab will be contacting the physician's office to obtain the necessary insurance information.

Some of the information on the insurance card may be the same as the information required on the form portion of the specimen collection kit. The information must still be entered onto the form to ensure accuracy for reporting of test results, since billing information may be entered at a different time and by different people than enter the demographic information required for reporting of test results.

Submitters may already be using a variety of internal processes and methods to expedite the accurate completion of the requested information, prior to collection of blood specimens. Here are some general tips for completing the revised screening forms:

- Use dark (preferably black) ball point pen, and press hard enough so that it is possible to read the bottom copy.
- Do not use a typewriter, as this can easily contaminate or bend the filter paper circles (blood collection site).
- Do not use the patient's plastic imprint card.
- Complete the required information on the form before collecting the blood specimen to avoid contamination of the blood collection site.
- At all times, avoid touching the area within the filter paper circles.
- Avoid contact of the filter paper circles with other surfaces.

The following 5 pages contain a copy of a Newborn Screening Form, and directions for proper completion of the form.


Newborn Screening 1st SPECIMEN
Date / Time Stamp
Baby Name (Last, First) 1
Date of Birth 2
Time of Birth 3
Birth Weight 4
Specimen Date 5
Time of Collection 6
Current Weight 7
Sex 8
Method of Collection: 9 Heelstick (preferred) Venipuncture
AHCCCS#: 10
Med. Rec. #: 11
12 Single Birth Multiple Birth (circle one) A B C D
Race 13
Food Source 15
Status 16
Hispanic 14
Accession Number: 18
Submitter / Physician Information
AZ 021110507
Submitter Name: 19
Submitter ID: 20
Physician Name (Last, First): 21
Physician ID: 22
Physician Address: 23
City, State, Zip: 24
Mother's Information
Mother Name (Last, First): 25
Date of Birth: 26
SS#: 27
Street Address: 28
City, State, Zip: 29
Telephone #: 30
Maiden Name: 31
Mother AHCCCS #: 32
33 Parent Refused Testing
DO NOT WRITE IN THIS SPACE
Expires 4 – 1 – 2004
S & S® 903™
LOT # W-001 AZ 021110507
L-8930501
AZ * 0 2 2 1 1 0 5 0 7 *
Newborn Screening 2nd SPECIMEN
Date / Time Stamp
Baby Name (Last, First)
Date of Birth
Time of Birth
Birth Weight
Specimen Date
Time of Collection
Current Weight
Sex
Method of Collection: Heelstick (preferred) Venipuncture
AHCCCS#:
Med. Rec. #:
Single Birth Multiple Birth (circle one) A B C D
Race
Food Source
Status
Hispanic
Accession Number:
Submitter / Physician Information
AZ 022110507
Submitter Name:
Submitter ID:
Physician Name (Last, First):
Physician ID:
Physician Address:
City, State, Zip:
Mother's Information
Mother Name (Last, First):
Date of Birth:
SS#:
Street Address:
City, State, Zip:
Telephone #:
Maiden Name:
Mother AHCCCS #:
Parent Refused Testing
DO NOT WRITE IN THIS SPACE
Expires 4 – 1 – 2004
S & S® 903™
LOT # W-001 AZ 022110507
L-8930501
AZ * 0 2 2 1 1 0 5 0 7 *

DISPLAY ONLY

ARIZONA NEWBORN SCREENING PROGRAM

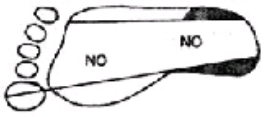
The State of Arizona requires that a Newborn Screening test be ordered for all infants born within the state. The specimen should be collected at 72 hours of age or prior to discharge, whichever comes first. Second Newborn Screens are required for all infants; Second Newborn Screen specimens should be collected between 7 and 14 days of age, or at the 1st doctor visit.

Specimen Collection Kit Instructions

Legibly print all information requested.

- Cord blood is not acceptable
- Invalid results may occur on specimen collected:
  - prior to 24 hrs after protein intake
  - prior to 36 hrs of age
  - from infants of low birth weight, receiving antibiotics, or having transfusion

Instructions for Heel Stick Specimen Collection



1. Place leg lower than level of the heart. Warm infant's foot (temperature no higher than 42°C) to increase circulation.
2. Disinfect skin with alcohol (not Betadine) and allow to air dry.
3. Puncture the skin in one continuous motion using a sterile lancet to a depth no greater than 2.0 mm. Use sterile gauze to wipe away the first drop of blood since it may be contaminated with disinfectant or tissue fluids.
4. Allow the second drop to form by free flow of blood.
5. Touch the drop of blood to the center of the filter paper circle. Fill each circle by a single application of the collection paper to a large drop of blood.
6. DO NOT APPLY BLOOD TO BOTH SIDES. Make sure each circle is completely filled.
7. Air dry blood spots in a horizontal position for at least three hours. Protect specimen from contamination while drying. Do not stack.
8. Make sure patient information on form is complete and legible.
9. Mail specimen within 24 hours of collection to:

   Arizona State Laboratory Services
   1520 W. Adams
   Phoenix, AZ 85007-2605

10. Order additional kits by calling 602-542-1190.

Special Collection Precautions

- Do not touch filter paper with ungloved hands
- Do not squeeze or milk specimen site
- Do not write on filter paper
- Do not use EDTA preserved blood
- Avoid contamination with glove powder
- Avoid layering blood

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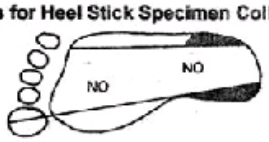

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2. Disinfect skin with alcohol (not Betadine) and allow to air dry.
3. Puncture the skin in one continuous motion using a sterile lancet to a depth no greater than 2.0 mm. Use sterile gauze to wipe away the first drop of blood since it may be contaminated with disinfectant or tissue fluids.
4. Allow the second drop to form by free flow of blood.
5. Touch the drop of blood to the center of the filter paper circle. Fill each circle by a single application of the collection paper to a large drop of blood.
6. DO NOT APPLY BLOOD TO BOTH SIDES. Make sure each circle is completely filled.
7. Air dry blood spots in a horizontal position for at least three hours. Protect specimen from contamination while drying. Do not stack.
8. Make sure patient information on form is complete and legible.
9. Mail specimen within 24 hours of collection to:

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- Do not touch filter paper with ungloved hands
- Do not squeeze or milk specimen site
- Do not write on filter paper
- Do not use EDTA preserved blood
- Avoid contamination with glove powder
- Avoid layering blood

INSTRUCTIONS FOR COMPLETING INFORMATION ON THE NEWBORN SCREENING SPECIMEN COLLECTION KIT

1	Baby Name (Last, First)	Enter the last name of the infant. This may not always be the same as the last name of the mother (or the father). Use the birth record or birth certificate name, if known. Enter the baby's first name, if known. If the first name is not known, enter Baby Boy or Baby Girl. In the case of multiple births, you may enter, Twin A, Twin B, or Baby Boy A, Baby Girl B, Baby Boy C, etc.
2	Date of Birth	Enter the baby's date of birth, in "mm/dd/yy" format.
3	Time of Birth	Enter baby's time of birth, using military time or noting AM/PM. For example, if the time of birth is 7:25 AM, it would be entered as "0725" or "7:25 AM." If the time of birth is 8:15 P.M. it would be entered as "2015" or "8:15" with PM circled.
4	Infant's Birth Weight	Enter the infant's birth weight in grams. If the birth weight cannot be obtained in grams, you may provide pounds and ounces, but clearly mark the form by circling "LBS/OZ".
5	Specimen Date	Enter the calendar date on which the specimen was taken, in "mm/dd/yy" format. For example, June 13, 2003 should be entered as "06/13/03."
6	Time of Collection	Enter the time in hours and minutes at which the specimen was collected, preferably in military time. For example, collection at 7:25 AM would be entered as "0725". Collection at 8:15 P.M. would be entered as "2015" or "8:15" with PM circled.
7	Current Weight	Enter the infant's current weight in grams. If the birth weight cannot be obtained in grams, you may provide pounds and ounces, but clearly mark the form by circling "LBS/OZ".
8	Sex	Mark the appropriate box to indicate the infant's gender.
9	Method of Collection	Mark the box that states how the specimen was collected.
10	AHCCCS #	Enter the infant's AHCCCS ID # if it is known. If the infant's AHCCCS ID # is not known, leave this space blank, but enter the Mom's ID #, if she is enrolled in AHCCCS, at the lower right as Mother's AHCCCS #.
11	Med. Rec. # (Medical Record Number)	Enter the infant's Medical Record Number.
12	Single or Multiple Birth	Mark the appropriate box, and circle the appropriate birth order (A, B, C, D) or enter appropriate letter for multiple births. Write which multiple (twin, trip, quad, etc.).
13	Infant's Race	Mark the box that identifies the infant's ethnic group. If unknown, mark the box that identifies the mother's ethnic group.
14	Hispanic	Mark the box that indicates whether the infant is of Hispanic origin.

INSTRUCTIONS FOR COMPLETING INFORMATION ON THE NEWBORN SCREENING SPECIMEN COLLECTION KIT

15	Food Source	Mark the box that identifies the infant's source of nutrition (breast milk, lactose formula, soy formula or a combination).
16	Status	Mark the box that best represents the status of the infant at the time of collection for each situation or condition listed.
17	Date Last Transfused	If the infant was transfused, enter the date of the latest transfusion. This information is needed to determine if the tests for some disorders are valid.
18	Accession Number	**FOR LAB USE ONLY. DO NOT PLACE STICKERS OR WRITING IN THIS AREA.**
19/ 20	Submitter Name and ID #	Enter the name of the agency/entity submitting the specimen for testing and the unique submitter ID code for that submitter. (If you do not have a submitter ID, call the Newborn Screening Data Entry Section at (602) 542-1187.)
21	Physician Name	Enter the physician's last name and first name. This is the physician who will receive information about test results and whose ID should be listed next.
22	Physician ID	Enter the physician ID of the infant's pediatrician. If the infant's pediatrician is not known, or the mother has not chosen a pediatrician for the infant yet, enter the attending practitioner of record. This is the physician who will receive information about test results. (If the practitioner does not have an ID, please contact the Newborn Screening Data Entry Section at (602) 542-1187.)
23	Physician Address	Enter the street address of the physician named above. This is the address at which the physician will receive information about test results.
24	Physician City, State, Zip Code	Please see #23 above. Enter the city, state and zip code of the physician.
25	Mother Name (Last, First)	Enter mother's last and first names from the medical record. In cases where the infant's guardian is not the mother, it is also important to include the name of the guardian or person who may be contacted for follow-up on abnormal screening results.
26	Date of Birth	Enter the mother's birth date in "mm/dd/yy" format.
27	SS#	Enter the mother's social security number. In most cases this can be obtained from the medical record, or preadmission paperwork, social security card, or the mother's Arizona driver's license.
28	Street Address	Enter the mother's street address or mailing address. If there is not a street address or mailing address, enter an address at which the mother can receive mail.
29	City, State, Zip	Enter the city, state and 5- or 9-digit zip code where the mother resides, even if the mother does not reside in Arizona, but the birth occurred in Arizona.

INSTRUCTIONS FOR COMPLETING INFORMATION ON THE NEWBORN SCREENING SPECIMEN COLLECTION KIT

30	Telephone #	Enter the mother's telephone number, including the area code. If the mother does not have a valid phone number, enter a number where the mother can always be contacted (work, friend, relative, etc.). This is important so the mother can be reached if there are abnormal results.
31	Maiden Name	Enter the mother's maiden name (birth record last name of the mother).
32	Mother AHCCCS #	Enter the mother's AHCCCS # if the mother is enrolled in AHCCCS.
33	Parent Refused Testing	Mark the box if the parent refuses to have the infant screened. The completed form, along with a copy of the signed refusal form, should be submitted to the State Lab.

5.5 Factors Affecting Test Results or Interpretation

There are several factors that can affect the analytical interpretation of a newborn screening test specimen of otherwise acceptable quality. Some of these circumstances cannot be avoided; that is why it is critical that the newborn screening forms be properly completed. Refer to section 5.4 for instructions on how to properly complete the newborn screening forms. This information provides the State Lab with important additional information for evaluating screening results. These factors include, but are not limited to:

- Gestational age of the infant
- Timing of the screening test
- Source of blood used for the test
- Whether the infant is receiving IV fluids or hyperalimentation
- Whether the infant has received a transfusion or dialysis
- Amount and type of protein (breast milk or formula) intake
- Antibiotic therapy

There are several ways in which practitioners or specimen collectors can minimize the incidence of certain factors that can alter a newborn screening test result:

- In sick or premature newborns that are hospitalized, do the first newborn screening test before a transfusion and, ideally, at 48-72 hours of life. It must be done by 7 days of age. T4 results may be abnormally low in premature infants.
- The screening specimen should be obtained before any transfusion of blood or blood products. The amount of enzymes/hormones in normal donor blood may be sufficient to affect galactosemia, hypothyroidism, and biotinidase assays, resulting in a false negative result. Donor red blood cells may also alter the screening outcomes for hemoglobinopathies.
- Collect capillary blood for the screening specimen utilizing the direct application method from the infant's heel (Refer to Section 5.10). If an alternative collection technique is to be used, refer to Section 5.14.
- Optimally, infants should receive protein (breast or bottle feedings) for 24-36 hours before the test. The tests for PKU, homocystinuria and MSUD may give false negative results if the infant has not had the opportunity to metabolize food before a specimen is collected. If a baby is discharged before 24 hours, then the test should be done at discharge. A second screening is required for all infants between one and two weeks of age or at the time of the first visit to the primary care physician.
- Specimens should not be collected from the same lines used to deliver hyperalimentation (TPN) or drugs. High levels of amino acids are present in

hyperalimentation, and antibiotics may interfere with the interpretation of the assays for MSUD and homocystinuria.

5.6 Use of Universal Precautions

Universal precautions should be observed when collecting any blood specimens. Specimens from any infant could be infected with human immunodeficiency virus (HIV) or hepatitis B virus (HBV). Blood collection techniques should be followed to minimize the risk of infection to any personnel who are responsible for collecting newborn screening specimens. Proper blood collection technique includes the use of gloves, and disposal of lancets in a biohazard container for sharp objects.

5.7 Tips for Ensuring Specimen Quality and Acceptability

The State Lab will screen specimens for quality and acceptability before the specimen is analyzed. If a specimen is unsatisfactory, it will be rejected, and another specimen must be collected. The accuracy of the screening test results is compromised if an unsatisfactory specimen is tested. Timely availability of analytical results is critical to early detection and treatment of disorders. Delays in testing, or the need for retesting, may cause an unnecessary burden and trauma to the infant and parents, or contribute to a missed case, if follow-up is not successful.

The State Lab will reject in advance of testing any samples that would likely provide unreliable, misleading, or clinically inaccurate values for the particular analytes being tested. The State Lab will notify the submitter by phone, then in writing, of their unsatisfactory specimen, and request an acceptable specimen be obtained and sent to the State Lab for testing as soon as possible.

Refer to the NCCLS Chart on page 5-16 for examples of acceptable and poor quality specimens. <u>The Lab will reject specimens when</u>:

- The quantity of blood is not sufficient for testing.
- The filter paper circles are not uniformly saturated with blood.
- The specimen appears to be contaminated by a spill or a foreign substance.
- The filter paper has been damaged or torn (for example, by rubbing capillary tubes over the surface of the filter paper).
- Blood has been applied to both sides of the filter paper.
- Tissue fluid or serum has separated from the blood.
- Blood clots are present on the specimen.
- Blood fixed by heat or age will not elute from the filter paper.
- There are uneven or multiple applications of blood to the filter paper circles.
- The specimen was mailed before it dried (a minimum of 4 hours).

- There is no blood on the filter paper and the "Parent Refused Testing" box was not checked.
- More than two weeks have elapsed between collection and receipt by the State Lab.
- The filter paper is not attached to the rest of the collection kit.

5.8 Source of Blood

Capillary blood obtained from the infant's heel is the standard source of blood to be used for newborn screening blood specimens. Venous blood obtained from dorsal hand veins is discouraged. Because of the differences in analyte concentration of capillary and venous blood, test readings may vary, so it is important to indicate on the specimen collection kit if venous blood was used. More analysis is needed before it can be determined if these variations are clinically significant. Also, hand veins may be needed for IV administration, and should be avoided for specimen collection.

Refer to the NCCLS Chart located on page 5-16. This chart illustrates the proper location for collecting the blood specimen from the infant's heel. Blood must be collected from the infant's heel using the most medial or lateral portion of the plantar surface of the heel (where "medial" is closest to the midline of the body, "lateral" is away from the midline of the body, and "plantar" is the walking surface of the foot).

BLOOD MUST <u>NOT</u> BE OBTAINED FROM THE FOLLOWING AREAS:

- Cord blood
- Umbilical artery catheters or central lines
- Previous puncture sites
- Curvature of the heel
- Central area of the foot (arch area)
- Fingers
- Toes

Puncture wounds to the central area of the foot may cause injury to nerves, tendons, and cartilage. Standard lancets may easily damage bones of fingers and toes, and result in local infection and gangrene.

5.9 Site Preparation and Puncture

The preferred method for collection of the blood specimen utilizes the heelstick method, with direct application of blood drops to the filter paper circles. The following technique is recommended for site preparation and skin puncture. Also refer to the NCCLS Chart located on page 5-16.

1. **Warm the skin puncture site.** A warm, moist towel wrap to the heel (no higher a temperature than 42º C) for approximately 3 minutes will increase the blood flow to the site significantly, without burning the skin.
2. **Place the infant's heel in a dependent position (lower than the heart).** This will increase the venous pressure and improve blood flow.
3. **Cleanse the site with an alcohol swab.** Use a 70% isopropyl alcohol swab. Wipe away any excess alcohol with dry sterile gauze, and allow the skin to air-dry. Any alcohol residue left on the skin can dilute the specimen and adversely affect the test result.
4. **Puncture the skin with a sterile lancet.** Puncture to a depth of 2.0 to 2.4 mm using a lancet size of 2.4 to 2.5 mm. In small premature infants, use as shallow a puncture as possible; punctures deeper than 2.4 mm may risk bone damage.
5. **Wipe the first drop of blood away with a sterile gauze pad.** The first drop of blood contains a higher concentration of tissue fluids that may dilute the specimen, and adversely affect the test result.

5.10 Direct Application Technique for Blood Collection

The following technique is recommended for direct application of blood drops to the preprinted circles on the blood specimen collection forms. Remember to lift the cover flap from the filter paper before applying the blood to the filter paper.

1. **Touch the filter paper directly to a large drop of blood from the heel.** Do not use the first drop of blood. The blood drop should be sufficiently large to soak through the filter paper completely.
2. **Examine both sides of the filter paper to ensure that the blood has penetrated and saturated the paper.** Proper filling and saturation of the circles will ensure that a sufficient quantity of blood has been collected for testing.
3. **Saturate each of the preprinted circles with blood**. A complete newborn screening specimen requires all the circles to be filled. However, for a recall specimen (testing for only one disorder), only 3 circles need to be filled.
4. **Elevate the infant's heel and apply pressure to the puncture site.** After the sample has been collected, elevate the heel, and apply pressure to the site with a sterile gauze pad or cotton swab until the bleeding stops. It is not advisable to apply adhesive bandages over puncture sites in newborns.

Inappropriate techniques may cause rejection of the specimen as unsatisfactory by the Arizona State Lab before the test is performed. Here are some practices that will enhance specimen quality and reduce the possibility of specimen rejection.

- Apply blood to only one side of the filter paper. Blood application to both sides of the paper invalidates quantitative analysis of the specimen. These specimens cannot be tested and a second specimen will have to be collected and submitted.
- Do not milk or squeeze the puncture site. Milking and squeezing may cause hemolysis in the specimen and increase the concentration of tissue fluids in the specimen. Hemolyzed specimens cannot be tested and a second specimen will have to be collected and submitted.
- Do not layer repeated applications of blood onto the circles. Layering, or successive applications of blood in the same printed circle, causes caking of the blood specimen, and/or nonuniform application of blood. These specimens cannot be tested and the submitter will be asked to repeat the specimen collection. If blood flow to the heel diminishes so that the circles cannot be easily filled with a single drop of blood, it is best to repeat the entire sampling technique at a new site.

5.11 Drying of Specimens

Once the specimen is collected on the filter paper, the entire specimen should be allowed to air dry in a suspended horizontal position (face up) for at least 4 hours at room temperature. Do not cover the specimen with the paper flap until the blood spots are thoroughly dry. Other important tips for drying specimens include:

- Avoid direct sunlight, or direct heat sources (procedure lamps, infant warmers, etc.).
- Avoid extremes of temperature (do not refrigerate specimens).
- Specimens should not be heated, stacked, or allowed to touch other surfaces during the drying process.
- Do not place specimens in sealed plastic bags or other closed containers.

5.12 Specimen Storage Precautions

All specimens should be thoroughly dry before they are packaged for mailing or delivery to the State Lab. Cross contamination of the specimens can also occur when collection forms are stacked directly on top of each other without the protective flap covering the blood specimen.

- When batch stacking cannot be avoided, the blood spots on the cards should be arranged so that they are rotated at a 180 degree angle from the blood spots immediately above and below in the stack. See page 5-18 for an example of how to package specimens when batch stacking cannot be avoided.
- Paper mailers are sufficient for all specimens. Specimens should not be placed in plastic mailers unless there are desiccant and humidity indicator cards included.

Humidity should be maintained below 30 percent. Humidity and moisture can affect the stability of the dried blood spot specimens.

- Chemicals or other types of specimens should not be packaged in the same container for shipment.

5.13 Procedures for Mailing Specimens

All newborn screening specimens must be sent to the State Lab within 24 hours of collecting the specimen. The address for mailing or courier delivery of all specimens is:

THE ARIZONA STATE LABORATORY
NEWBORN SCREENING
1520 WEST ADAMS STREET
PHOENIX, ARIZONA 85007-2698

RECEIVING:
Phone: (602) 542-1190

Courier delivery is strongly encouraged when it is possible or practical. The State Lab's Receiving Unit is located at the north side of the building.

5.14 Alternative Techniques for Blood Collection (Not the Preferred Method)

The following techniques are alternatives to the direct application method for blood collection. These are not preferred techniques, but may produce acceptable specimens for testing.

Capillary tube application from heel puncture source

Blood may be collected in sterile heparinized capillary tubes from the heel puncture site. The blood from the capillary tube may then be applied directly to the filter paper circles. The tip of the heparinized capillary tube (100µL size) should be touched to the drop of blood formed at the puncture site. Use a fresh capillary tube for each blood spot that will be collected on the filter paper. Do not use EDTA or citrate anticoagulants because they will interfere with the assays. After filling the capillary tube to the calibration mark, invert the tube several times to mix the contents, and then immediately apply the blood to the center of the preprinted circle on the filter paper.

"Coloring in" the circle, repeated dabbing around the circle, tapping the tube on the filter paper, or any technique that can scratch, indent, or compress the filter paper should not be used. These specimens will be rejected prior to testing. Be sure to apply blood from the tubes to the circles as soon as possible. Waiting too long may allow red cells and plasma to separate, causing an unsatisfactory specimen.

Capillary tube application from dorsal hand vein source

Blood may be collected in sterile heparinized capillary tubes from the needle puncture of a dorsal hand vein. After the venipuncture, the procedure for collecting and applying blood from capillary tubes may be followed. The blood from the capillary tube may then be applied directly to the filter paper circles. Using capillary tubes for this type of specimen collection increases the risk that samples may be rejected for tearing, scratching, or trauma to the filter paper. Use of capillary tubes also adds an additional risk of specimen rejection due to plasma separation, especially if there is any delay in applying the blood to the filter paper.

APPENDIX A

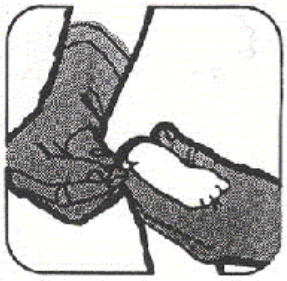
HOW TO COLLECT AN ACCEPTABLE BLOOD SPOT SPECIMEN

1.0 SAMPLING TECHNIQUE

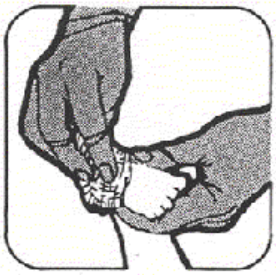
1.1 Cleanse infant's heel with 70% isopropyl alcohol (use only rubbing alcohol).

1.2 Allow heel to air dry.

1.3 The puncture should be made within the shaded area in the drawing above.



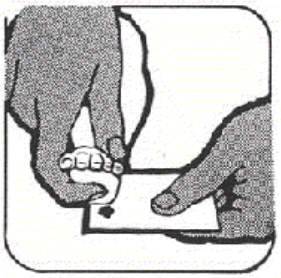
1.4 Using lancet provided, perform puncture as illustrated.
WEARING GLOVES



1.5 Gently wipe off first drop of blood with sterile gauze or cotton ball. (Initial drop contains tissue fluids which may dilute sample).

1.6 Wait for spontaneous free flow of blood.

1.7 Apply gentle pressure with thumb and ease intermittently as drops of blood form.



1.8 Touch printed side of filter paper card to the blood drop and fill each printed circle with a SINGLE application of blood. Observe the saturation of each printed circle as the blood flows through the filter paper. Spotting should be done *only* on the printed side.

1.9 Allow blood specimen to AIR DRY THOROUGHLY, on level non-absorbent open surface, such as a plastic-coated test tube rack, *for 2–6 hours* at ambient temperature (Do not stack or heat).

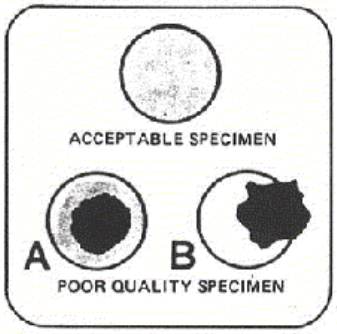
1.10 Place *dried filter paper* in mailing envelope provided for this purpose.

2.0 PITFALLS

2.1 Failure to wipe off alcohol residue may dilute the specimen and adversely affect test results.

2.2 Puncturing the heel on posterior curvature will permit blood to flow away from puncture, making proper spotting difficult. DO NOT LANCE ON PREVIOUS PUNCTURE.

2.3 *Milking* or squeezing the puncture may cause hemolysis and admixture of tissue fluids with specimen.



2.4 Do not layer successive drops of blood on the circle spot (Example A). If blood flow diminishes to incompletely fill circles, REPEAT sampling technique 1.1 thru 1.10. Note Example B for poor quality specimen with inadequate blood.

2.5 Avoid touching area within circle before collection and blood spots after collection on filter paper. Do not allow water, feeding formulas, antiseptic solutions, etc. to come into contact with the sample.

2.6 Do not place filter paper in the envelope until thoroughly dry.

2.7 INSUFFICIENT DRYING ADVERSELY AFFECTS TEST RESULTS.

PROFESSIONS GOVERNMENT INDUSTRY

NATIONAL COMMITTEE for CLINICAL LABORATORY STANDARDS

NCCLS VOL. 12 NO. 13

State Laboratory: Newborn Screening

1520 W. Adams
Phoenix, AZ 85007-2698
(602) 542-1190
(602) 542-0760 FAX

REQUEST FOR MATERIALS

Agency Code/Name: ____

Address _________________________City ________________AZ Zip________

Person Ordering______________________ Phone________________________

Enter the number of supplies needed next to the items listed below:

ITEM REQUESTED	QUANITY
Linked Newborn Screening Collection Kit	
Supplemental Newborn Screening Collection Kit	
Envelopes (white – for collection kits)	
Neonatal Nursery Envelopes (brightly colored)	
Specimen Collection Instruction Posters	
UPS Prepaid Labels	
UPS Overnight Letter Mailer	
Request for Materials Form	

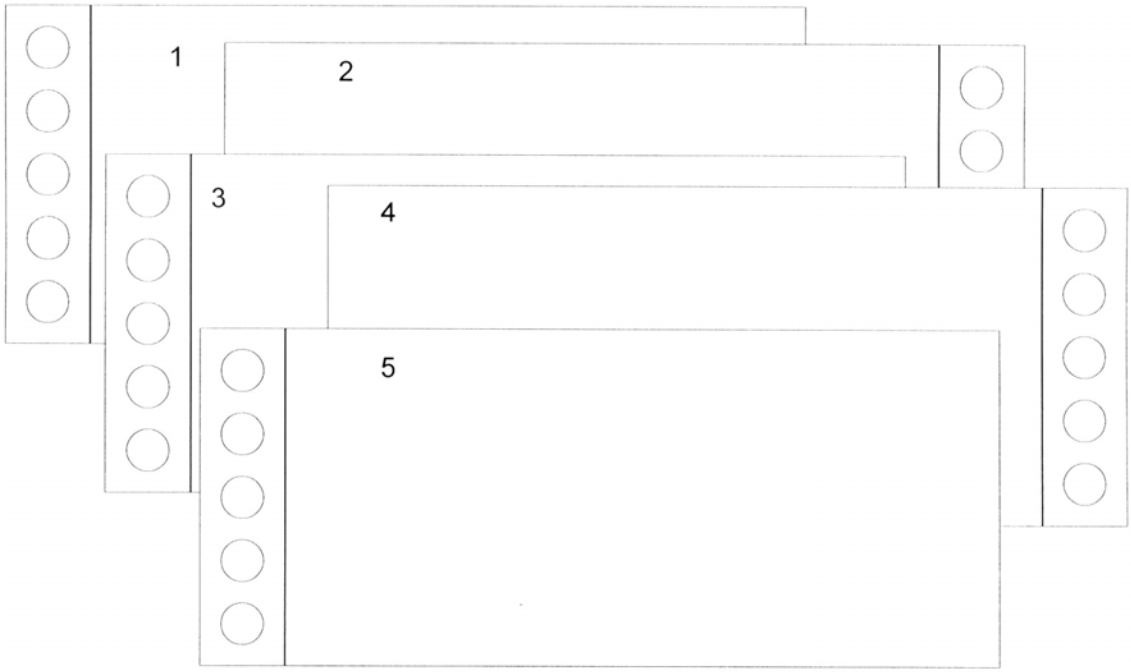
FOR STATE LABORATORY USE ONLY
DO NOT WRITE BELOW THIS LINE
****

Order Received______________________ Shipped by

____

Ship Method ____________________ Date Shipped __________________________

How to package newborn screening specimens when batch stacking cannot be avoided



CHAPTER 6
COMMUNICATION, COORDINATION, AND FOLLOW-UP OF SCREENING RESULTS

CHAPTER 6
COMMUNICATION, COORDINATION, AND FOLLOW-UP OF SCREENING RESULTS

6.1 Introduction

This chapter describes the Newborn Screening Program's policies and guidelines for coordinating communication with physicians and parents, and contains program procedures for monitoring, follow-up, and documentation of screening results. The primary purposes of Newborn Screening Program follow-up activities are to: 1) promptly notify physicians of abnormal screens; 2) link physicians to appropriate specialty consultation services; and 3) verify that infants with abnormal screening results are under a doctor's care. The notification procedures represent recommended courses of action, and are by no means the only steps that may be taken to locate parents and practitioners. Program staff utilize available information and resources to expedite contact and are responsible for documentation of all follow-up calls and contact.

The mechanisms by which physicians can obtain copies of the newborn screening results of their patients are also delineated. The Newborn Screening Program is available to assist physicians in verifying that their patients have had a newborn screening test as required by NBS rules.

6.2 General Responsibilities for Reporting and Follow-up

The Newborn Screening Program has developed a system for reporting and follow-up of screening results. This system focuses on timely and appropriate "information flow." Newborn screening information must be quickly and accurately reported to the persons who can expedite family contact, additional testing, and the initiation of treatment for affected infants. All parties, including the Program's Follow-up group, State Lab, practitioners, submitters and families, will need to work together to assure rapid response times and timely follow-up.

The State Lab reports the results of all newborn screening tests to practitioners by mail and to the Program's Follow-up staff by computer transfer and by phone (for highly abnormal results). The Follow-up staff is then responsible for coordinating urgent or emergency contact with practitioners, and for following up on all other abnormal or inconclusive results. The Newborn Screening Program Follow-up staff tracks all abnormal results until resolution or a diagnosis is confirmed in writing from a baby's physician or a specialist.

Practitioners are responsible for completing the information requested on the specimen collection kits, being sure to identify themselves and provide accurate contact information for parents. This contact information will be used by Follow-up staff to notify physicians and parents in case of an abnormal result. They also need to submit insurance information along with each second screen so that appropriate billing can be done. Practitioners also need to inform the program of their correct mailing addresses, phone and fax numbers.

Practitioners are also responsible for follow-up testing, diagnosis and treatment of infants with abnormal or borderline screens, or confirmed positive screens. Practitioners are responsible for coordinating with families to obtain second screen specimens from infants between 7 and14 days of age or at the first doctor visit after discharge from the hospital. Practitioners may request assistance from the Program's Follow-up staff if they are having problems in locating parents or obtaining repeat tests for infants. Follow-up staff will coordinate efforts with practitioners and other agencies to locate parents as soon as possible. If physicians order newborn screening test on infants who will not be continuing under their care, they may be contacted by Follow-up staff if the screen has an abnormal result. Follow-up staff will request that they contact parents and order further testing, unless another physician can be identified. Follow-up staff will not contact parents by phone unless they are unable to locate a physician.

The chart on the following page shows important reporting responsibilities and follow-up protocols for the Newborn Screening Program. Refer to Section 6.4 for specific follow-up procedures.

6.3 Chart of Reporting and Follow-up Guidelines for Newborn Screening Results

	ABNORMAL RESULT	BORDERLINE RESULT	NORMAL RESULT	UNSATISFACTORY SPECIMEN
REPORTED TO	Program by State Lab Practitioner by Program Submitter by State Lab Practitioner by State Lab Parent by practitioner	Program by State Lab Practitioner by Program Submitter by State Lab Practitioner by State Lab Parent by practitioner	Program by State Lab Submitter by State Lab	Submitter by State Lab
HOW RESULT IS REPORTED	Phone call and certified letter to practitioner with instructions for action	Phone call and/or certified letter to practitioner from Program with instructions for action	Routine mail	State Lab phone call to submitter, written notification, and instructions for action
RESPONSIBILITY FOR OBTAINING ADDITIONAL TEST SPECIMEN	Practitioner	Practitioner	N/A	Submitter
RESPONSIBILITY FOR FOLLOW-UP WITH FAMILY	Practitioner Program sends certified letter to parent	Practitioner Program may send certified letter to parent	Practitioner	Submitter and practitioner
TIMEFRAME FOR COLLECTION OF FOLLOW-UP TEST SPECIMEN	Within 48 hrs of notification	Within 48 hrs of notification	N/A – second screen must still be collected	Within 48 hrs of notification
OTHER ACTION TO BE TAKEN	Consult with specialist as appropriate. Start appropriate treatment or dietary restriction, pending confirmation. However, for most cases, treatment is not begun unless infant is symptomatic, or unless the condition is confirmed.	Start appropriate treatment or dietary restriction if appropriate	N/A--initiate additional testing or treatment if infant becomes symptomatic	Identify potential opportunities for training of staff who are collecting newborn screening specimens

6.4 Requests for Resubmission of Initial Screen Due to Unsatisfactory Specimen

Section 5.7 provides tips for ensuring the quality of the screening specimens. The State Lab will reject all screening specimens that cannot be tested. In such cases, the State Lab will place a telephone call or send a fax to the submitter to request another specimen. In addition, the State Lab will send a computerized mailer to the submitter, noting the reason for the rejected specimen**.** The submitter (if different from the practitioner) will need to contact the practitioner and arrange for the test to be redrawn from the infant. The State Lab will send a reminder letter if another specimen is not received within two weeks.

6.5 Reporting of Normal Newborn Screen Results

If the newborn screening test is within normal limits, the State Lab will send a computerized mailer reporting the test results to the submitter and/or the practitioner of record. The practitioner is encouraged to share these results with parents.

6.6 Reporting of Abnormal Newborn Screen Results

If the State Lab identifies an abnormal or borderline result for one or more of the eight disorders on the screening panel, the State Lab will report those results to the Program. The State Lab also sends a computerized mailer reporting test results to the submitter and/or the practitioner of record.

The Program's Follow-up staff will notify the practitioner listed on the specimen collection kit of the abnormal result. If the practitioner of record is not the baby's health care provider, Follow-up staff will attempt to identify the current provider and notify him/her of the abnormal results. (See 6.10 and 6.11) In addition, the Program will also send written notification via certified letter to the practitioner and parent/guardian. The practitioner should contact the parent/guardian and arrange for the repeat or confirmation tests to be performed. During this process, the Program's Follow-up staff can assist practitioners in finding the parents and in coordinating consultation and special medical services. Practitioners should expect that Newborn Screening Follow-up staff or contracted specialists will telephone them to provide assistance regarding appropriate follow-up treatments and procedures. Depending upon the type of disorder, it may be necessary to initiate treatment as soon as possible, without waiting for confirmation.

6.7 Medical Record Documentation

Hospitals must ensure that results of newborn screening tests are documented in the infant's birth record. As mentioned in Section 3.9, a parent's refusal to submit a newborn screening specimen must be clearly documented in the medical record. The completed specimen collection kit with the parent refusal box checked (without blood) must be submitted to the State Lab.

Practitioners are required to verify that a newborn screening test was done for all babies under a year of age in their care. Practitioners are also responsible for making sure that abnormal results and follow-up are documented in the infant's medical record.

6.8 On Call System for Newborn Screening Program Medical Consultants

The consultation contract for Newborn Screening Program Medical Consultants requires that the consultants be available 24 hours a day, 7 days week. Physicians who provide guidance and medical consultation to the Newborn Screening Program must provide acceptable and appropriate alternate coverage for these services when they are unavailable. Physician consultants and practitioners must provide their staff or answering service with updated telephone or pager numbers to facilitate timely contact in the case of a neonatal emergency.

6.9 Parent/Family Communication Guidelines

When an infant has a highly abnormal screen that requires immediate confirmation and follow-up, the practitioner/physician of record is contacted first. The infant's physician then contacts the parent to arrange for any additional testing or required medical follow-up. In cases where the physician cannot be located, or where the identity of the physician is not known and other resources are not available, Newborn Screening Program staff may need to contact parents to identify the infant's physician.

The following guidelines are used by Newborn Screening staff in communications with parents and families:

1. When necessary, Newborn Screening staff attempt to contact the mother listed on the Newborn Screening form and speak directly with her or they baby's legal guardian. Staff use professional judgment in leaving telephone messages or relaying information through persons other than parents.
2. Newborn Screening staff approach all communication with parents in a professional, reassuring, and supportive manner. They use clear, simple language, and avoid using highly technical terms.

3. The Newborn Screening Program can arrange translation services, when required, if a parent does not speak English. Some of the Newborn Screening staff are bilingual (Spanish/English) and can speak directly to Spanish-speaking parents. In some situations, staff may need to communicate with parents through another family member or friend who can translate.
4. Staff will identify themselves clearly and state the purpose of the call. For example: I am Mary Smith from the Newborn Screening Program at the Arizona Department of Health Services. I am calling about _____.
5. The Program's Follow-up staff as a general rule, DO NOT GIVE OUT LAB RESULTS TO PARENTS OVER THE PHONE. They report lab results only to authorized personnel at the physician's office, or to contracted specialists. If a parent calls the Newborn Screening Program about a test result, they answer general questions that parents may have about "next steps" in the follow-up process, but defer any discussion about specific lab results or interpretation to the infant's physician.
6. Staff may make phone calls to the parent/guardian to identify the baby's doctor (because the original doctor contacted was not the baby's doctor). In cases where the parent does not have or know a doctor for the baby, Newborn Screening staff may need to work with the parent to identify a physician for follow-up reporting of laboratory test results. If necessary, they may inquire about the baby's medical insurance plan. The plan may have an assigned doctor for the baby, even if the mother has not chosen a doctor yet. Newborn Screening staff may also refer parents to AHCCCS, low-cost clinics or other health services. They inform the parent that the Newborn Screening staff will call the chosen doctor's office to report the laboratory test and that the doctor or nurse should be calling them directly to give instructions for what to do next.

6.10 Notification Guidelines

The Newborn Screening Program maintains confidentiality of reported test results and other protected health information, including demographic information provided by submitters on the newborn screening form and information obtained by the Program's staff during follow-up activities. The NBS program has procedures to maintain confidentiality and ensure that access to protected health information is limited only to those authorized to receive it.

Abnormal or Borderline Results

When a newborn screening lab result is abnormal for a disorder, the infant's physician and parent/guardian are notified, so that further testing, proper care and follow-up can be arranged. Standard letters are generated from the computer database by the Program's Follow-up staff and are sent via certified mail (with return receipt) to the baby's physician and to the mother/guardian.

As a general guideline, highly abnormal results are first reported via telephone to the infant's physician. The submitter and physician of record are the "first tier" of contact for the reporting of abnormal results. When possible, Newborn Screening staff report highly abnormal screening results directly to the infant's physician. The physician is then required to contact the parent/guardian to arrange for follow-up.

Inconclusive Results

In the case of an inconclusive result, a certified letter is sent to the baby's physician of record requesting further testing. A letter is not usually sent to the parents. Inconclusive results often occur with the tests for homocystinuria and MSUD if the baby received antibiotics before a specimen was collected. In such a circumstance, further testing is required on a new specimen in order to obtain a valid result.

Hemoglobin Traits

Hemoglobin testing is done primarily to identify babies who have hemoglobin diseases, particularly sickling diseases. In the process, carriers of these diseases are identified. These individuals are said to have hemoglobin traits. If the newborn screening test result indicates the possibility of a hemoglobin trait, letters are sent to the physician of record and to the parents. The parents are requested to identify the baby's health care provider so a subsequent letter can be sent to the identified physician.

Complicating Factors

Although this is the desired process, actual circumstances may require flexibility and creativity on the part of staff to find and link physicians and parents. Coordinating this location and notification may be difficult due to many factors, including, but not limited to:

- An on-call doctor or hospitalist is listed as the baby's doctor on the specimen collection kit
- A doctor is not listed or an incorrect doctor is listed on the specimen collection kit
- Parents do not have a doctor for the baby
- Parents do not have a telephone
- Parents' telephone number is incorrectly listed or disconnected
- Parents/family have moved and there is no forwarding address
- Parent/guardian does not have an address
- Guardianship of the infant has changed
- The infant's name has changed

6.11 Documentation of Follow-Up of Abnormal Screening Results

For each infant who has an abnormal or highly abnormal initial screen, the Newborn Screening Program conducts follow-up activities to document aspects of the infant's ongoing care, diagnostic confirmation, and treatment. The program follow-up staff sends a standard Final Diagnosis/Treatment Plan form to the practitioner for those babies with abnormal results on both newborn screening tests or with a highly abnormal result on either screen for other than metabolic disorders (that is, for thyroid disorders, CAH or hemoglobinopathies). The metabolic geneticist sends in diagnosis forms for the metabolic disorders. The practitioner completes and returns the form, reporting the final diagnosis for the infant, date treatment was initiated, diagnostic tests performed, referrals to specialists, and any treatment or follow-up plan implemented.

6.12 Case Closure

One of the primary responsibilities of the Newborn Screening Program follow-up staff is to ensure that infants with abnormal test results are under a physician's care. Follow-up staff track and monitor the status of open newborn screening cases. These cases include those involving any inconclusive, abnormal or highly abnormal results. The goal of this process is to identify and notify a practitioner who will be caring for the infant, in order to confirm a diagnosis and initiate early treatment. If a parent or guardian refuses follow-up for an infant with a positive screen, referrals may be made to public health agencies, social service agencies, public safety officials, or child protective service representatives.

Once a disorder is confirmed or ruled out through subsequent testing, the case is closed. Cases may also be closed when repeated attempts to contact the parent/guardian have failed, and when all reasonable means of contact have been exhausted.

6.13 Reporting of Test Results via Facsimile

In circumstances where written documentation of diagnostic test results is required for the program, the Newborn Screening program may request that a fax of the test report be sent to the Newborn Screening Program's dedicated fax line, (602) 364-1495. The fax machine for the Program is located in close proximity to Newborn Screening Staff.

The Newborn Screening Program is pleased to assist health care providers in obtaining newborn screening test results for babies entering their practice. A practitioner can fax a request on letterhead including the name, date of birth and mother's name of the baby to the Newborn Screening Program at (602) 364-1495. Program staff will look up, print off and fax results back to the provider's office.

Conversely, if test results are faxed from the Newborn Screening Program to practitioners or contracted specialty physicians, measures are instituted to ensure that these results and identifying information are viewed only by authorized persons.

CHAPTER 7
PROGRAM FEES AND PAYMENT PROCEDURES

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7.1 Testing Fees

Arizona's Newborn Screening Test consists of two screens, both of which are mandatory. Each of the screens (**First Screen** and **Second Screen**) costs **$20**.

First Screen

The First Screen is billed to and paid for by the submitter (generally a hospital, birthing center or midwife) who sends the first specimen for a baby that is satisfactory for testing by the State Lab.

Second Screen

The Second Screen may be billed to and paid for by hospitals, midwives, insurance companies, patients or any other qualified public or private persons. If a physician's office or an intermediate laboratory, which collected the specimen on physician's orders, sends in a specimen, it is vital that the State Lab receive the patient's complete insurance information, if applicable, with the newborn screening specimen. If this information is not received, staff from the State Lab will contact physicians and facilities to obtain this information.

Recall Test: No charge

Recall tests for individual disorders are performed in response to an abnormal or borderline result on a previous screen. There is no fee for these tests. This designation, as well as the disorder for which there was a prior abnormal test result, must be marked on the specimen collection kit or it will be considered to be a billable specimen.

Unsatisfactory specimen: No charge

A specimen is deemed unsatisfactory if it could provide unreliable, misleading, or clinically inaccurate values for the particular analytes being tested, as determined by State Lab procedures. The practitioner who sends such a specimen (or causes such a specimen to be sent) to the State Lab is notified by phone and by letter that the specimen was unsatisfactory. They are required to ensure that another specimen is collected and submitted for testing, as soon as possible after being notified.

7.2 Payment to the Department

The Department will bill for First and Second Screens at least monthly. Payments are due to the Department within 30 days of the billing date.

Payments should be sent to:

Arizona Department of Health Services
Newborn Screening Program
P.O. Box 25046
Phoenix, Arizona 85002-5046